Endocrine Journal 1994, **41** (5), 535–540

Pituitary Function in Patients with Rathke's Cleft Cyst: Significance of Surgical Management

KUNIKI EGUCHI, TOHRU UOZUMI, KAZUNORI ARITA, KAORU KURISU, TAKASHI YANO, MASAYUKI SUMIDA, AKIHIKO TAKECHI, AND BASANT PANT

Department of Neurosurgery, Hiroshima University School of Medicine, Hiroshima 734, Japan

Abstract. The pituitary function of patients with Rathke's cleft cyst before and after surgery was investigated to clarify the significance of surgery and operative indications. The authors have treated 19 patients with Rathke's cleft cyst. There were panhypopituitarism in 2 patients (11%), amenorrhea and/or galactorrhea in 3 (16%), diabetes insipidus in 4 (21%), and visual disturbance in 9 (47%). All the patients underwent systematic endocrinological examination and were found to have various degrees of pituitary dysfunction. Panhypopituitarism was endocrinologically confirmed in 2 patients. Hyperprolactinemia was observed in 4. These patients underwent aspiration of the cyst contents and biopsy of the cyst wall.

Postoperative follow-up endocrinologic evaluation performed more than 3 months after surgery showed improvement in pituitary function in 9 out of 13 patients (69%). Amenorrhea and/or galactorrhea recovered or improved in 100% of patients and visual disturbance improved in 89%. However, diabetes insipidus and panhypopituitarism did not improve postoperatively, in any patient.

The results of the present study indicate that the incidence of pituitary dysfunction in patients with Rathke's cleft cyst is higher than suspected and in most cases surgical intervention improves pituitary function and the clinical status of the patient. Therefore, surgical treatment is recommended even when the patient has only mild symptoms or signs, including pituitary dysfunction, to prevent irreversible panhypopituitarism.

Key words: Amenorrhea, Diabetes insipidus, Panhypopituitarism, Pituitary function, Rathke's cleft cyst

(*Endocrine Journal* **41:** 535–540, 1994)

RATHKE'S CLEFT CYSTS (RCCs) are now detected with increasing regularity as a result of modern neuroimaging techniques. Together with visual disturbance and headache, pituitary dysfunction was a common clinical presentation in patients with RCC [1–3]. However detailed endocrinological evaluation of patients with RCC has not been performed. This study describes pituitary function in RCC before and after surgery.

Received: February 7, 1994
Accepted: June 10, 1994
Correspondence to: Dr. Kuniki EGUCHI, Department of Neurosurgery, Hiroshima University School of Medicine, 1–2–3 Kasumi, Minami-ku, Hiroshima 734, Japan

Subjects and Methods

A retrospective study of patients with RCC treated in our department and other affiliated institutions between May, 1979 to October, 1993 was conducted. There were 19 patients in our series: 10 men and 9 women, with a mean age of 45 years (range, 17 to 74 years).

The mean duration of symptoms was 3 years and 2 months (longest, 25 years). Before surgery, these patients underwent endocrine studies including growth hormone (GH) and cortisol responses in an insulin tolerance test (0.1–0.15 U/Kg body), thyrotropin (TSH) and prolactin (PRL) responses in TRH test (500 μg/body) and luteinizing hor-

mone (LH) and follicle stimulating hormone (FSH) responses in LHRH test (100 μg/body).

All patients were treated surgically and had operative and/or histopathological verification. All but three patients had histological verification of RCC. In these three patients, it was difficult to obtain a specimen of the Rathke's cleft cyst wall. However, the clinical, radiologic, and operative findings were similar in these patients to the histologically verified patients. Operative verification was performed by identifying a thin-walled cyst and its mucinous contents.

Thirteen patients underwent follow-up endocrinological evaluation for more than 3 months after surgery. Impaired pituitary hormone secretion was defined as a low basal value and/or response to hormonal stimulation [4]. The revised criteria for normal basal values and normal responses to stimuli used in this study are shown in Table 1. As secretion of ACTH is known to be episodic, ACTH was evaluated indirectly by measuring the serum cortisol level. The location of the pituitary gland was determined from the position of the neurohypophysis which was demonstrated as a high-intensity area on T1-weighted images and the entire pituitary gland which enhanced strongly on Gd-DTPA [5].

Statistical analyses of differences between pituitary function before and after surgery were performed by a Wilcoxon signed rank test.

Results

Table 2 summarizes the clinical and radiographic features. Among the presenting features, visual disturbance was present in 9 patients, headache in 7, general fatigue in 4, polyuria in 4, and amenorrhea in 3 of 19 patients. Visual disturbance was manifested as a visual field defect in 8 and decreased visual acuity in 6 patients. A history of diabetes insipidus (DI) was present in 4 patients, of whom one recovered spontaneously before admission (Patient 2). Except in one case, every cyst arose from the sella. Five were entirely intrasellar and 13 had intrasellar as well as suprasellar extension. Only one cyst was entirely suprasellar (Patient 11).

Table 3 shows results of endocrine studies. Pituitary dysfunction was defined as having impairment of more than 2 anterior pituitary hormones. This was present in 100% of the patients. Obvious clinical panhypopituitarism was present in 2 patients and these patients showed impairment of 5 to 6 pituitary hormones on endocrine studies (Patients 1 and 2).

Preoperative endocrinological evaluation showed impaired secretion of FSH in 16 (84%), GH in 15 (79%), cortisol in 13 (68%), PRL in 10 (53%), LH in 6 (32%) and TSH in 5 (26%) of the patients. There existed a correlation between the number of impaired pituitary hormones and age or size of the cyst.

Table 1. Criteria of normal basal value and normal response in endocrine studies

Hormone		Basal value	Response[a]	Test
GH	(ng/ml)	<5.0	≧17.0	Insulin tolerance test
Cortisol	(μg/dl)	6.4–18.8	≧15.9	(0.1-0.15 U/Kg body)
TSH	(μU/ml)	0.4–5.0	≧8.0	TRH test (500 μg/body)
Prolactin	(ng/ml)	1.5–9.7[b]	≧15.0	
		1.4–14.6[c]		
LH	(mIU/ml)	1.8–5.2[b]	≧30.0	LHRH test (100 μg/body)
		1.0–34.9[d]	≧30.0	
		8.7–38.0[e]	≧140	
FSH	(mIU/ml)	2.9–8.2[b]	≧5.0	
		2.0–14.8[d]	≧5.0	
		26.2–113.3[e]	≧48.0	

[a)]Twofold increase in the value is a prerequisite. [b)]Male; [c)]Female; [d)]Reproductive woman; [e)]Postmenopausal woman.

Table 2. Summary of the clinical and radiographic features of 19 patients with Rathke's cleft cyst

Patient No.	Age	Sex	Symptoms	Location of cyst	Cyst size (mm)	Location of pituitary gland	Cyst contents
1	70	M	General fatigue Polyuria	I & S	23×20×16	Below	Whitish mucus
2	63	M	Headache, General fatigue Cold intolerance	I & S	18×17×16	Above	Whitish mucus
3	74	M	Visual disturbance	I & S	20×16×18	Anterior	Whitish mucus & waxy nodule
4	70	F	Visual disturbance	I & S	22×16×15	Anterior	Superior cyst: xanthochromic Inferior cyst: whitish mucus
5	67	F	Headache, Visual disturbance	I & S	16×15×14	Below	Thick milky, CSF-like
6	63	M	Visual disturbance	I & S I & S	20×16×17	Anterior	Transparent mucus
7	60	F	Visual disturbance	I & S	19×13×23	Anterior	Xanthochromic fluid
8	58	F	Headache, Visual disturbance	I & S	24×16×18	Surrounding	Whitish mucus
9	48	F	General fatigue, Polyuria	Intrasellar		Anterior	Whitish mucus
10	43	M	Visual disturbance	I & S	14×16×26	Anterior	Milky fluid
11	40	M	Headache	Suprasellar	9 × 9 ×12	No translocation	CSF-like
12	37	M	General fatigue	I & S	26×20×12	Posterior	Xanthochromic fluid
13	35	F	Amenorrhea, Galactorrhea	I & S	14×14×22	Anterior	Milky fluid
14	32	F	Headache, Cold intolerance Amenorrhea, Visual disturbance	I & S	28×26×23	Surrounding	Whitish mucus
15	26	F	Headache	Intrasellar	19×16×20	Above	Xanthochromic mucus
16	22	M	Polyuria	Intrasellar	6 ×10× 4	Anterior	Whitish mucus
17	21	F	Amenorrhea, Galactorrhea	Intrasellar	12×18× 5	Surrounding	Xanthochromic fluid
18	17	M	Visual disturbance	I & S	19×17×14	Anterior	Whitish mucus
19	17	M	Headache	Intrasellar	10× 8× 7	Unknown	Milky fluid

Cyst size is presented as height × width × length. I & S, intrasellar and suprasellar; CSF, cerebrospinal fluid.

Two patients, a male and a postmenopausal woman, had incidental hyperprolactinemia (Patients 5 and 6). Three patients presented with amenorrhea, of whom two had hyperprolactinemia (Patients 13 and 17) and one had gonadal hypofunction (Patient 14).

All 19 patients were treated surgically, 4 transcranially and 15 transsphenoidally. Removal of the cyst contents and biopsy of the cyst wall were performed in those operations. No complication due to surgery occurred. In 11 out of 19 patients the cyst contained whitish mucus and in others it was either xanthochromic or CSF-like.

Histopathological verification of RCC was possible in 16 patients, but it was doubtful in 3 patients (Patients 4, 13 and 17, Fig. 1). Specimens from these 3 patients contained part of the anterior lobe of the pituitary, mucoid debris, and connective tissue, respectively. In 4 patients (Patients 1, 7, 11 and 16) inflammatory cells were seen in the adenohypophysis adjacent to the cyst wall (Fig. 1). During surgery every lesion was found to be cystic in nature with a thin wall and containing thick, milky fluid. Radiological findings were similar in both groups irrespective of histological verification of RCC.

Nine patients with visual disturbance improved or recovered within 1 month of surgery (88%) and 3 patients with amenorrhea also improved rapidly. Postoperative endocrinological evaluation revealed that pituitary function deteriorated temporarily, however, improved significantly in most patients during the follow-up period (Table 3). However, patients with obvious clinical panhypopituitarism required postoperative administration of hydrocortisone and thyroxine, and those with DI did not improve and continued to require desmopressin (as of the recent follow-up visit, Patients 1, 9 and 16).

The mean follow-up period in this study was 24 months. Recurrence was observed in one patient (Patient 7) who had undergone removal of the cyst contents and biopsy of the cyst wall by the transsphenoidal approach during the first operation. In the second operation she underwent, again, removal of cyst contents and cyst wall bi-

Table 3. Results of endocrine studies of 19 patients with Rathke's cleft cyst

Patient No.	GH B	GH A	Cortisol B	Cortisol A	TSH B	TSH A	PRL B	PRL A	LH B	LH A	FSH B	FSH A	No. of impaired hormones before surgery	No. of impaired hormones after surgery[a]	No. of normalized hormones
1	L	ND	L	ND	N	ND	L	ND	L	ND	L	ND	5	ND	
2	L	L	L	L	L	L	L	L	L	L	L	L	6	6	0
3	N	N	L	L	N	N	L	N	N	N	L	L	3	2	1
4	L	N	L	N	N	N	N	N	L	L	L	L	4	2	2
5	L	N	N	N	N	N	H	H	N	N	L	L	3	2	1
6	L	ND	N	ND	L	ND	H	ND	N	ND	N	ND	3	ND	
7	L	L	L	N	N	N	N	N	L	L	L	L	4	3	1
8	L	L	N	N	N	N	N	N	N	N	L	L	2	2	0
9	L	L	L	N	L	N	N	N	L	N	L	L	5	2	3
10	L	L	L	L	N	N	L	L	N	N	L	L	4	4	0
11	L	ND	N	ND	N	ND	N	ND	N	ND	L	ND	2	ND	
12	N	N	N	N	L	L	N	N	N	N	L	L	2	2	0
13	L	ND	L	ND	N	ND	H	ND	N	ND	N	ND	3	ND	
14	L	N	L	N	N	N	L	N	L	N	L	L	5	1	4
15	L	ND	L	ND	N	ND	N	ND	N	ND	L	ND	3	ND	
16	N	N	L	L	L	L	L	N	N	N	L	L	4	3	1
17	L	N	N	N	N	N	H	N	N	N	N	N	2	0	2
18	L	L	L	L	N	N	L	N	N	N	L	L	4	3	1
19	N	ND	L	ND	N	ND	L	ND	N	ND	L	ND	3	ND	
B[b]	15		13		5		10		6		16				
A[c]		3		4		1		4		2		0			

[a] Differences from numbers before surgery, $P=0.006$. [b] Total number of patients with impaired pituitary hormones before surgery. [c] Total number of patients with normalized pituitary hormones after surgery. B, before surgery; A, after surgery. N, normal basal value and normal response; H, high basal value or hyperresponse; L, low basal value or hyporesponse; ND, not done.

opsy by craniotomy. Further, she had an Ommaya reservoir installed. There was no recurrence as of 13 months after surgery.

Discussion

With the advent of MRI, asymptomatic or subclinical Rathke's cleft cysts (RCCs) are now detected with increasing regularity [5, 6]. The operative indications are unclear in those patients [2]. However, no detailed endocrinological evaluation of patients with RCC has been performed. For these reasons, patients with RCC pituitary dysfunction and change of pituitary function after surgery were studied.

Incidence of pituitary dysfunction: Pituitary dysfunction, visual disturbance and headache are the most common symptoms in patients with RCC [1, 2, 7]. Preoperatively, we found obvious clinical panhypopituitarism in 2 patients and a certain degree of anterior pituitary dysfunction in every one of 19 patients who underwent systematic tests of pituitary hormone release. Voelker *et al.* and Ross *et al.* reported hypopituitarism in 60 (39%) of 155 patients and in 5 (12%) of 43 patients [1, 2]. Our endocrinologic data revealed a higher incidence (100%) of hypopituitarism than reported and a similar percentage (32%) of patients with symptoms of hypopituitarism. Therefore, subclinical hypopituitarism in patients with RCC is more common than suspected.

Amenorrhea is also a common symptom in female patients with RCC that is caused by hyperprolactinemia resulting from compression of the pituitary stalk [8] and also by impairment of gonadotropins, i.e. LH and FSH, reflecting relatively severe pituitary dysfunction.

Pathomechanism of pituitary dysfunction: RCC is thought to be a lesion of the pars intermedia [9] that may cause pituitary dysfunction [1]. In causing pituitary dysfunction in patients with RCC, mechanical compression of the pituitary gland by the cyst may play a major role [2]. However, there

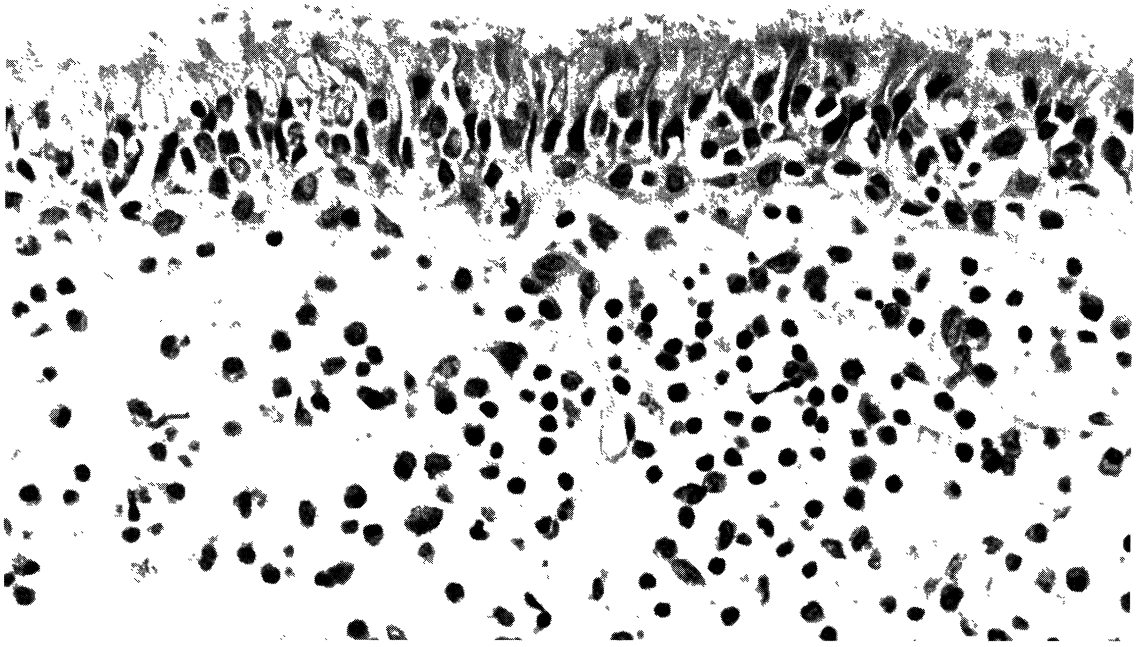

Fig. 1. Wall of Rathke's cleft cyst in Patient 2. The lining consists of ciliated columnar cells. Inflammatory cells are seen beneath the columnar cells and pituitary gland (hematoxylin and eosin stain, magnification ×300).

are other mechanisms by which pituitary dysfunction may be caused, because even intrasellar RCCs, which do not seem to have high pressure, cause not merely hypopituitarism but DI. In addition, inflammatory change of the pituitary gland was observed in 4 patients in our series. Therefore, inflammation, as well as mechanical compression, of the pituitary gland may play an important role in causing pituitary dysfunction in patients with RCC. The pathogenesis of inflammatory change may involve the leakage of cyst contents into the pituitary gland, however this is uncertain.

Significance of surgery: Visual disturbance and headache recover relatively soon after surgery [1–3, 10]. On the other hand pituitary dysfunction recovers gradually. This improvement is thought to be due to decompression of the pituitary gland and probably due to the improvement of inflammation in the adenohypophysis. In contrast, panhypopituitarism or DI does not recover even after surgery, implying that pituitary dysfunction is irreversible in patients whose pituitary is too severely injured.

Menstruation resumed after surgery as pituitary function improved. In patients with hyperprolactinemia, normalization of the serum PRL level and recovery of menstruation can also be expected relatively soon after surgery [1–3, 8].

Surgical indications for RCC: Considering the risk of deterioration of pituitary function during the course of this disease, surgical treatment is generally recommended even when the patient has mild symptoms or signs, e.g. headache, mild visual field defect and increased PRL, and a cyst size of more than 10 mm [2]. For small and asymptomatic RCC, it is generally recommended that the patient be followed up with MRI unless clinical symptoms and signs appear. In addition, we recommend regular, once a year, systematic endocrinological examination. If pituitary function worsens, surgical intervention should be considered.

Our patients were surgically treated either by the transsphenoidal approach or craniotomy. Re-

cently, the transsphenoidal approach has become preferred to craniotomy as it is less invasive and is not associated with aseptic meningitis [1, 2, 11]. RCC can be treated successfully with removal of the cyst contents and marsupialization of the wall [12]. This procedure is superior to simple drainage which has a higher recurrence rate [1–3]. Also, radical removal of the cyst should be avoided to avert further damage that may decrease the probability of pituitary function recovery after surgery [1, 2, 13, 14].

Acknowledgements

We thank Tamotsu Kitaoka, M. D., Junji Goishi, M. D., Katsuaki Sakoda, M. D., Takeshi Shima, M. D., Mitsuo Yamamoto, M. D. and Kazutoshi Mukada, M. D. for providing the use of materials on patients.

References

1. Voelker JL, Campbell RL, Muller J (1991) Clinical, radiographic, and pathological features of symptomatic Rathke's cleft cysts. *J Neurosurg* 74: 535–544.
2. Ross DA, Norman D, Wilson CB (1992) Radiologic characteristics and results of surgical management of Rathke's cysts in 43 patients. *Neurosurg* 30: 173–179.
3. Midha R, Jay V, Smyth HS (1991) Transsphenoidal management of Rathke's cleft cysts. A clinicopathological review of 10 cases. *Surg Neurol* 35: 446–454.
4. Uozumi T, Mori S, Watanabe M, Takimoto N, Mogami H, Azukizawa M, Hashimoto T, Miyai K, Kumahara Y (1974) Endocrinological evaluation of sellar and suprasellar tumor cases—the first report —on preoperative pituitary function. *No Shinkei Geka* 2: 389–394.
5. Sumida M, Uozumi T, Mukada K, Arita K, Kurisu K, Eguchi K (1994) Rathke cleft cysts: Correlation of enhanced MR and surgical findings. *Am J Neuroradiol* 15: 525–532.
6. Keyaki A, Hirano A, Llena JF (1989) Asymptomatic and symptomatic Rathke's cleft cysts. Histological study of 45 cases. *Neurol Med Chir (Tokyo)* 29: 88–93.
7. Yoshida J, Kobayashi T, Kageyama N, Kanzaki M (1977) Symptomatic Rathke's cleft cyst. Morphological study with light and electron microscopy and tissue culture. *J Neurosurg* 47: 451–8.
8. Trokoudes KM, Walfish PG, Holgate RC, Pritzker KPH, Schwartz ML, Kovacs K (1978) Sellar enlargement with hyperprolactinemia and a Rathke's pouch cyst. *JAMA* 240: 471–473.
9. Iwasaki Y (1992) Histological diagnosis of brain tumors: (22) Arachnoid cyst and Rathke's cleft cyst. *No Shinkei Geka* 20: 625–634.
10. Barrow DL, Spector RH, Takei Y, Tindall GT (1985) Symptomatic Rathke's cleft cysts located entirely in the suprasellar region: review of diagnosis, management, and pathogenesis. *Neurosurgery* 16: 766–772.
11. Yamamoto M, Jimbo M, Ide M, Umebara Y, Hagiwara S, Kubo O (1993) Recurrence of symptomatic Rathke's cleft cyst: a case report. *Surg Neurol* 39: 263–268.
12. Kiya K, Harada K, Mori S, Uozumi T, Itoh H (1981) Rathke's cleft cyst. A case report. *No Shinkei Geka* 9: 517–521.
13. Iraci G, Giordano R, Gerosa M, Rigobello L, Di Stefano E (1979) Ocular involvement in recurrent cyst of Rathke's cleft: case report. *Ann Ophthalmol* 11: 94–98.
14. Martinez LJ, Osterholm JL, Berry RG, Lee KF, Schatz NJ (1979) Trans-sphenoidal removal of a Rathke's cleft cyst. *Neurosurgery* 4: 63–65.