

# Symptomatic Rathke's cleft cysts: A report of 24 cases

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**ABSTRACT.** We review the clinical, hormonal and imaging features of 24 consecutive patients with symptomatic Rathke's cleft cysts (RCCs), and assess the long-term effectiveness and complications of transsphenoidal cyst removal. Out of 250 consecutive patients, 24 (10%) underwent endonasal transsphenoidal surgery for RCC; 19 (79%) were women. Symptoms at presentation included headaches (83%), hyperprolactinemia (38%), central hypothyroidism (21%), galactorrhea (13%), diabetes insipidus (13%), IGF-1 deficiency (13%), central adrenal insufficiency (8%) and visual loss (8%). In total, 37% of women had irregular menses and 60% of men sexual dysfunction and hypogonadism. Two girls presented with precocious puberty. Cyst size varied from 7 to 25 mm. Fifteen (60%) had a suprasellar component. Initial and 3-month post-operative imaging revealed complete cyst resection in 23 of 24 patients. Headaches resolved

in 65% of subjects and visual loss resolved in both patients who presented with this symptom. Of those presenting with endocrinopathy, 56% had improvement of at least one anterior pituitary axis; two subjects (8%), both with suprasellar RCC, developed a new hormone deficiency post-operatively and two subjects young girls, (8%) had RCC recurrence, one at 36 months after surgery, requiring a second operation, and the other had a small asymptomatic recurrence 6 months after surgery. In conclusion, RCC accounts for 10 % of surgically treated sellar and suprasellar masses. Headache, hyperprolactinemia, menstrual irregularities and sexual dysfunction are common presenting symptoms. Simple cyst removal via a transsphenoidal approach offers a safe and effective treatment. Cyst recurrence may be more common in children. (J. Endocrinol. Invest. 27: 943-948, 2004)

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## INTRODUCTION

The differential diagnosis of cystic sellar and suprasellar lesions includes craniopharyngioma, arachnoid cyst, epidermoid cyst, cystic pituitary adenoma, and Rathke's cleft cysts (RCC). The pathogenesis of RCC remains controversial: cuboidal or ciliated columnar epithelial cells line the majority of RCC, and the leading theory is that they represent remnants from the incomplete obliteration of Rathke's pouch during embryological development (1). However, since stratified squamous epithelial cells (like those typically seen in craniopharyngiomas) are sometimes noted to line a portion of RCC, some authors have speculated that simple RCC and complex crani-

opharyngiomas represent the two extremes of a continuum of cystic sellar lesions (2, 3).

Although autopsy studies indicate that approximately 20% of incidentally discovered pituitary lesions are RCC (4), symptomatic RCC have historically been felt to be uncommon. Symptomatic patients may present with headaches, visual disturbance, hyperprolactinemia and/or varying degrees of hypopituitarism. Such patients are generally managed by transsphenoidal drainage of the cyst and, to the extent possible, excision of the cyst wall. In this study, we report the clinical, hormonal and radiographic features of 24 consecutive patients with RCC, with special attention to the surgical and endocrinological outcome and recurrence rates.

## MATERIALS AND METHODS

### *Patient population*

Patients eligible for this study included those who underwent endonasal transsphenoidal surgery for sellar and suprasellar lesions at UCLA Medical Center between 1999 and 2003. The UCLA Pituitary Surgery database was queried for patients who underwent surgery for RCC and a retrospective chart review was performed. The study was reviewed and approved by the UCLA Institutional Review Board.

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Key-words: Rathke's cleft cysts, transsphenoidal surgery, endocrine recovery, surgical outcome.

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### Imaging, hormonal assessments and outcomes

RCCs were characterized based on pre-operative and post-operative magnetic resonance (MR) findings and categorized as: a) purely intrasellar, b) intrasellar/suprasellar or c) purely suprasellar. Figures 1-3 show representative examples of intrasellar, intrasellar/suprasellar and suprasellar RCC. Hormonal data included pre- and post-operative levels of serum PRL, morning serum cortisol and ACTH, TSH and free T4, IGF-1, total and free testosterone, serum so-

dium and urine specific gravity. Clinic notes were reviewed for pre- and post-operative visual status (visual acuity and visual field tests), report of headaches, menstrual/sexual history, and implementation of hormone replacement. Sexual dysfunction was defined as either low sexual libido and/or erectile dysfunction. The RCC diagnosis was confirmed by histological examination of the surgical material in each case. Complication rates were determined from the operative and post-operative notes.

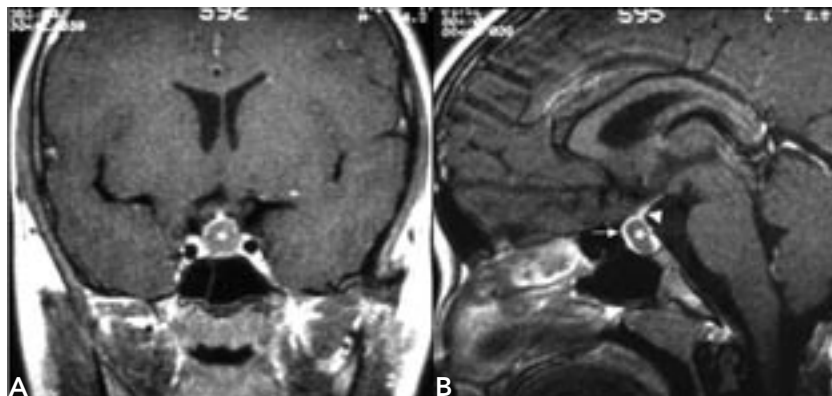


Figure 1 - Sellar magnetic resonance imaging (MRI) of an intrasellar Rathke's cleft cyst (RCC), after iv administration of gadolinium-DTPA. Coronal (A) and sagittal (B) images. The cyst (\*) appears as a homogeneous lesion with low signal intensity and without post-contrast signal enhancement. The arrow shows the normal pituitary gland displaced forward by the cyst; the arrowhead points to the pituitary stalk.

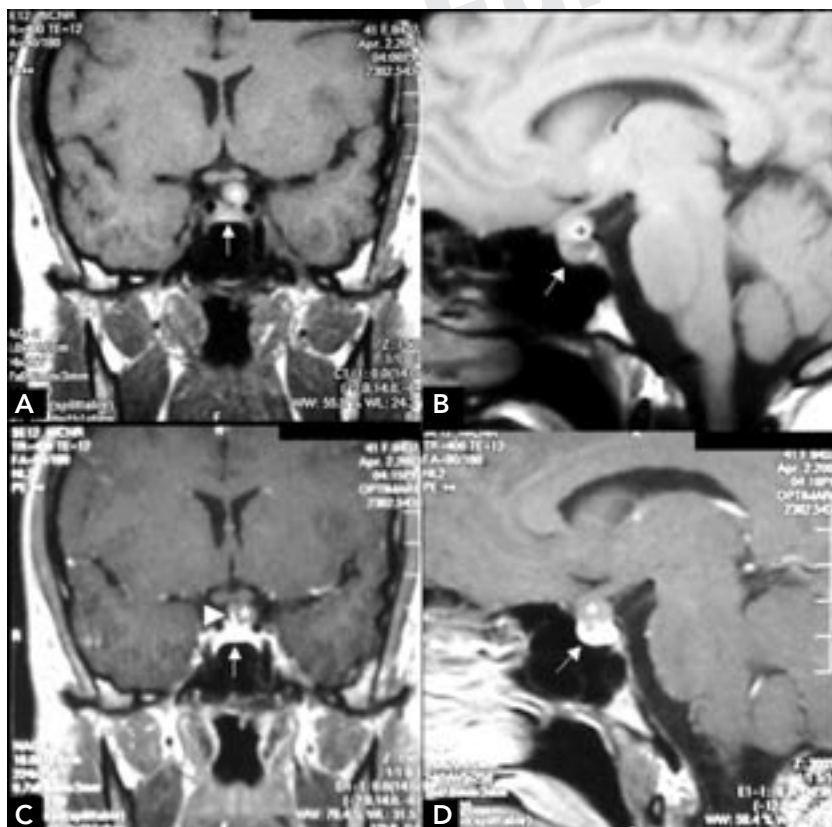


Figure 2 - Sellar magnetic resonance imaging (MRI) of a suprasellar Rathke's cleft cyst (RCC) before (A, B) and after (C, D) iv administration of gadolinium-DTPA. Coronal (A, C) and sagittal (B, D) images. The cyst (\*) appears as a homogeneous isointense lesion sitting atop the pituitary gland (arrow) and displacing the pituitary stalk to the right (arrowhead). The cyst does not enhance with gadolinium.

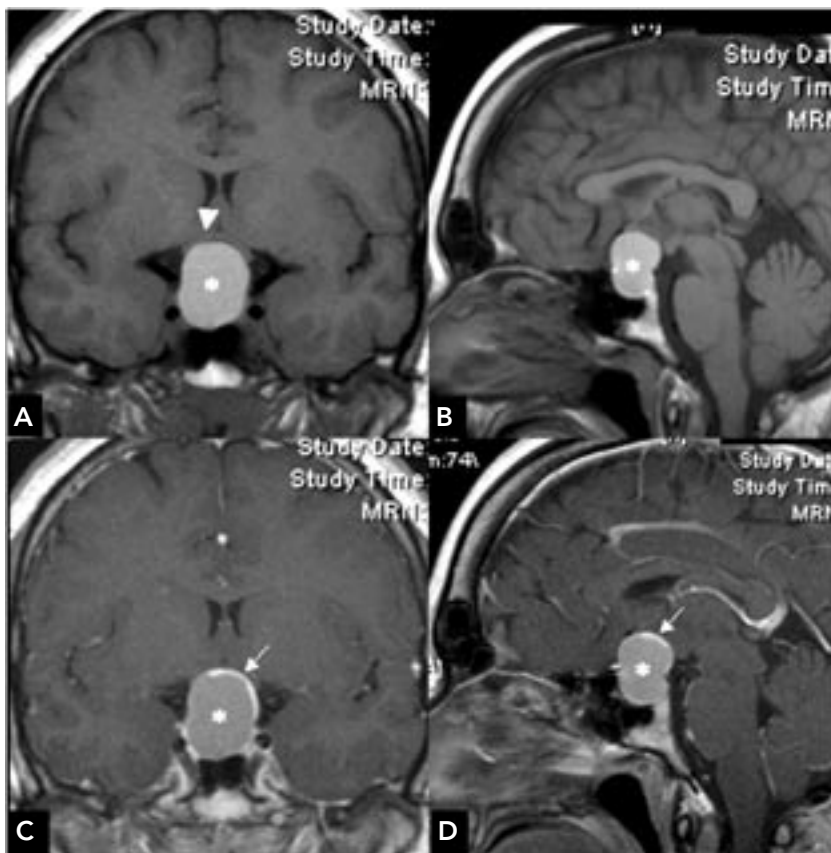


Figure 3 - Sellar magnetic resonance imaging (MRI) of an intra- and suprasellar Rathke's cleft cyst (RCC), before (A, B) and after (C, D) iv administration of gadolinium-DTPA. Coronal (A, C) and Sagittal (B, D) images. The cyst (\*) appears as a homogeneous slightly hyperintense, non-enhancing intra- and suprasellar lesion. The optic chiasm (arrowhead) is displaced upward. The normal pituitary gland (arrow) is compressed and displaced upward and to the left. Pre-operatively, the patient had panhypopituitarism.

### Surgical technique

All patients underwent RCC removal via a direct endonasal transsphenoidal approach with the operating microscope, as previously described by Zada et al. (5). Since intrasellar and intrasellar/suprasellar RCCs are typically located behind the anterior pituitary gland, their removal involves a direct approach through the anterior inferior pituitary gland via a low midline vertical glandular incision. Through this small working corridor the cysts are generally easily removed with suction, ring curettes and gentle irrigation. At the completion of cyst removal, the resection cavity is carefully inspected for residual cyst contents and cyst lining. An angled endoscope was used for assisted visualization in 4 of 24 cases. Given that the resection cavity generally consists of normal appearing anterior and posterior pituitary gland, no attempt was made to vigorously strip the cyst wall off of these normal structures. For purely suprasellar RCCs which were all intimately attached to the pituitary stalk and often embedded within the superior aspect of the anterior pituitary gland, the surgical approach was over the normal pituitary gland and below the diaphragma sellae in 4 cases, and above the diaphragma sellae in 2 cases.

If a small "weeping" cerebrospinal fluid (CSF) leak was present after cyst removal, the repair involved use of collagen sponge (Helistat; Integra Life-Sciences Corp., Plainsboro, NJ) and titanium mesh (MicroMesh 0.2 mm, Styker-Leibinger, Kalamazoo, MI); larger CSF leaks were repaired with abdominal fat, collagen

sponge and titanium mesh; large diaphragmatic leaks associated with removal of suprasellar RCCs also had a lumbar drain placed for 48-72 h of CSF diversion. For patients without an intra-operative CSF leak, only collagen sponge was placed and sellar floor reconstruction with mesh was not performed. Nine patients had a small intraoperative CSF leak and 6 patients had a large CSF leak. All patients with CSF leaks recovered fully without sequelae.

### RESULTS

#### Patient population

Of 250 consecutive patients undergoing pituitary surgery from 1999 to 2003, 24 (10%) had removal of a RCC. The majority of patients were females (79%) whose median age was 31 yr (range 8-61 yr). The median duration of follow-up was 17 months (range 7-57 months).

#### Presenting symptoms

Whereas headaches were present in the vast majority (83%) of patients with RCC, only a small minority (two patients, 8%) had visual disturbances. Abnormalities of the gonadal axis were the most common presenting endocrinopathy. Among the men, 60% had hypogonadotropic hypogonadism

with associated sexual dysfunction; 37% of women, had irregular menses; 38% of patients, hyperprolactinemia; and 13%, galactorrhea. The percentage of patients presenting with central hypothyroidism, IGF-1 deficiency, diabetes insipidus, central adrenal insufficiency were 21%, 13%, 13%, and 8%, respectively. The clinical picture in one subject was compatible with pituitary apoplexy. The patient initially presented with galactorrhea, irregular menses, and hyperprolactinemia and went on to develop worsening headaches, visual field loss, and complete anterior pituitary gland failure over a 1-week period. Two girls presented with precocious puberty and are reported separately (6). The presenting symptoms and hormonal findings are summarized in Table 1.

### Imaging findings

The maximal dimensions of the cysts (as measured in the coronal plane) ranged from 7 to 25 mm (mean 13+4 mm) but varied based on cyst location: in 54% of patients, the cyst was purely intrasellar and in 25% purely suprasellar. The remainder (21%), had both an intra- and suprasellar component.

### Surgical outcome

Post-operative clinical and biochemical data were available for all 24 patients. Headaches resolved in 13 out of 20 patients (65%) and visual loss resolved in both patients presenting with this problem.

Of those patients presenting with endocrinopathy, 56% had improvement of at least one anterior pituitary axis; hyperprolactinemia resolved in 56% of patients; normalization of menses occurred in 67% of women. Further evaluation of one subject with persistent menstrual irregularities after surgery disclosed clinical and biochemical evidence of the polycystic ovarian syndrome (PCOS). Among the 3 males presenting with hypogonadism, serum testosterone level normalized in one. However, all 3 males continued to have sexual dysfunction post-operatively.

### Surgical complications

There were no deaths attributable to surgery and no vascular injuries, visual worsening, or other cranial neuropathies; no post-operative CSF leaks, nasal-septal perforations or mucocoeles; and no pulmonary, cardiac, or septic complications. Two patients (a 29-year-old man with a sellar and suprasellar RCC and a 31-year-old woman with an intrasellar RCC) developed post-operative aseptic (chemical) meningitis that resolved without sequelae. All CSF cultures as well as testing for bacterial antigens were negative in both patients. New anterior hormone deficiency (namely, GH deficiency based solely on IGF-1 level and not confirmed by stimulation testing) occurred in 1 patient and new

persistent diabetes insipidus occurred in another subject; both of them had purely suprasellar RCCs that were intimately attached to the pituitary stalk. Endocrinological outcomes are summarized in Table 2.

Four patients (17%) developed delayed post-operative hyponatremia with serum sodium levels falling below 125 mmol/l. The median post-operative day of the sodium nadir occurred on post-operative day 7 (range 6-9 days). In one of these patients, the serum sodium dropped to 118 mmol/l and was associated with a brief seizure without sequelae. All patients were successfully treated with hypertonic (3%) saline, fluid restriction, and/or sodium urea infusion.

### Recurrence rate

Initial and 3-month post-operative MR imaging revealed complete cyst resection in 23 of 24 (96%)

Table 1 - Summary of presenting symptoms.

Presenting symptom	Proportion (%)
Headache	20/24 (83)
Hypogonadism (men)	3/5 (60)
Sexual dysfunction (men)	3/5 (60)
Irregular menses	7/19 (37)
Hyperprolactinemia	9/24 (38)
Central hypothyroidism	5/24 (21)
Galactorrhea	3/24 (13)
Diabetes insipidus	3/24 (13)
IGF-1 deficiency	3/24 (13)
Hypoadrenalism	2/24 (8)
Visual disturbance	2/24 (8)

Table 2 - Endocrinological recovery after surgery.

Symptom	Proportion (%) with recovery
Irregular menses	4/6 (67)*
Galactorrhea	2/3 (67)
Hyperprolactinemia	5/9 (56)
Hypogonadism (men)	1/3 (33)
Sexual dysfunction (men)	0/3 (0)
Central hypothyroidism	2/5 (40)
Hypoadrenalism	1/2 (50)
IGF-1 deficiency	1/3 (33)
Diabetes insipidus	1/3 (33)

\*Although 7 patients presented with irregular menses, one patient's menstrual disturbance was later determined to have resulted from polycystic ovarian syndrome (PCOS).

patients and partial removal in one patient. Two of 24 subjects (8%), with long-term follow-up developed RCC recurrence, both were young girls. The first patient, an 8-yr-old girl with precocious puberty, had an initial complete removal of a 1.5-cm intrasellar and suprasellar RCC; a 1-cm cyst recurrence was noted 36 months after her initial surgery. Given the size of the recurrence and the compression of the normal pituitary gland, she underwent repeat endonasal transsphenoidal resection. Although her initial post-operative MRI showed complete cyst removal, repeat MRI 6 months after her second surgery revealed another recurrence. She remains asymptomatic with normal hormonal function and is being monitored with repeat MRIs every 3 months. The second patient, a 10-yr-old girl with headaches and a 1.2-cm intrasellar RCC, had an asymptomatic cyst recurrence 6 months after surgery. She has normal pituitary function and is also being monitored with repeat MRIs every 3 months. Should further cyst enlargement be noted in either of these cases, repeat surgery will be recommended.

## DISCUSSION

### *Presenting symptoms*

Although it is generally believed that symptomatic RCCs are rare, our series indicates that they account for approximately 10% of surgically-treated sellar and suprasellar lesions. This rate falls between other comparable series. For example, Isono et al. (7) found 15 cases of RCC out of a total of 102 operative cases (15%). In the largest case series of histologically confirmed RCC published, el-Mahdy et al. (8) encountered a total of 28 RCCs in a series of approximately 400 pituitary-based lesions. Like these other reports, we found that symptomatic RCC predominantly occurred in women. However, this may simply reflect a detection bias as irregular menses often trigger an endocrine evaluation.

By far, the most common presenting symptom was headache. However, headache occurred in isolation only in 6 out of 24 (25%) patients. Of the six patients whose only presenting symptom was headache, this symptom resolved in all but one patient. It is possible that headache was unrelated to the RCC in the remaining one patient.

In the vast majority of subjects, headache was accompanied by an endocrine disturbance. As noted in other published series, we found a high rate of pituitary dysfunction (3, 7-11). Hyperprolactinemia was the most common endocrinopathy, occurring in nearly 40% of patients. Menstrual irregularity was a common finding in women, and all of the men reported sexual dysfunction. Other series have re-

ported high rates of GH deficiency in patients with RCC (10, 11). Voelker's literature review of approximately 150 RCC cases revealed that nearly 70% of patients under 18 yr of age had pituitary dwarfism (11). We used serum IGF-1 level as a surrogate marker of GH status. This likely underestimates the true rate of GH deficiency, since approximately one-third of adults with GH deficiency may have an IGF-1 level within the lower limits of normal (12). Ideally, provocative testing (either insulin-induced hypoglycemia or GHRH with arginine) should be used to assess GH secretory capacity. In Eguchi's surgical series of 19 RCC patients, the GH axis was systematically assessed with an insulin tolerance test (10). GH deficiency was defined as a GH response of <17 ng/ml. Based on this relatively liberal criterion, GH deficiency was seen in 79% of RCC patients. Since most authorities use a GH cut-point of <5 ng/ml after insulin-induced hypoglycemia to diagnose GH deficiency (13), we suspect that the true incidence of GH deficiency in this population likely falls somewhere between our findings (13%) and those of Eguchi (79%).

In addition to hyperprolactinemia and hypopituitarism, we also encountered several patients with precocious puberty and apoplexy, which are quite unusual but previously reported clinical presentations of RCC (6, 14).

### *Surgical outcome and complications*

Simple cyst removal via an endonasal transsphenoidal approach utilized in this series was safe and quite effective both in restoring endocrine function and alleviating symptoms of mass effect. Visual disturbance resolved in both of two patients, and over 65% of those presenting with headaches were free of headache post-operatively. There were no major post-operative surgical complications except two cases of aseptic meningitis.

After surgery, 56% of patients had an improvement in at least one anterior pituitary axis and only 2 patients developed a new hormonal deficiency post-operatively. Worth of note, both patients with new hormonal deficiencies had suprasellar RCCs that were intimately attached to the pituitary stalk, making their removal considerably more challenging.

The rate of delayed hyponatremia (17%) in this series was considerably higher than the 2-9% rate reported after transsphenoidal surgery for pituitary adenomas (15, 16). Delayed hyponatremia after pituitary surgery is generally attributed to the syndrome of inappropriate secretion of anti-diuretic hormone (SIADH). It is possible that a higher rate of hyponatremia after RCC surgery may result from the closer anatomical association of RCC with the pituitary stalk and neurohypophysis.

### Recurrence rate

After a median duration of 16 months of follow-up, only two patients (8%) developed a cyst recurrence. This low recurrence rate is in keeping with other large series (8). However, in one series of 12 patients (9), the recurrence rate was significantly higher (i.e., over 30%). Possible explanations for differences in recurrence rates may be attributable to our relatively short length of follow-up or possibly a result of misclassification of craniopharyngiomas as RCC in other series. Shin's systematic analysis of over 50 cystic sellar lesions provides strong evidence that there is considerable overlap in the clinical, biochemical and radiographic features of craniopharyngiomas and RCC (3). Although RCCs are more likely to have cuboidal or columnar epithelial lining and craniopharyngiomas are often lined by stratified squamous epithelium with keratin nodules and calcification, these authors point out that even histological analysis may sometimes fail to fully distinguish craniopharyngioma from RCC. Since the recurrence rates of craniopharyngiomas are significantly higher than RCC, misclassification can significantly bias recurrence rates. Interestingly, both recurrences in our series were in young girls. It is possible that in younger patients, the cyst linings are more active and prone to produce recurrent cysts than in older patients. More aggressive approaches to completely remove these cysts, beyond simple drainage, may be warranted. However, attempts to strip the cyst lining away from the anterior and posterior lobes would likely result in a higher rate of new hormonal deficiencies.

### CONCLUSION

Symptomatic RCCs account for approximately 10% of surgically treated sellar lesions. Headache, hyperprolactinemia, menstrual irregularities, sexual dysfunction and anterior pituitary gland failure are common presenting symptoms. Although longer follow-up is needed, simple cyst removal via an endonasal transsphenoidal approach is a safe and effective treatment.

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