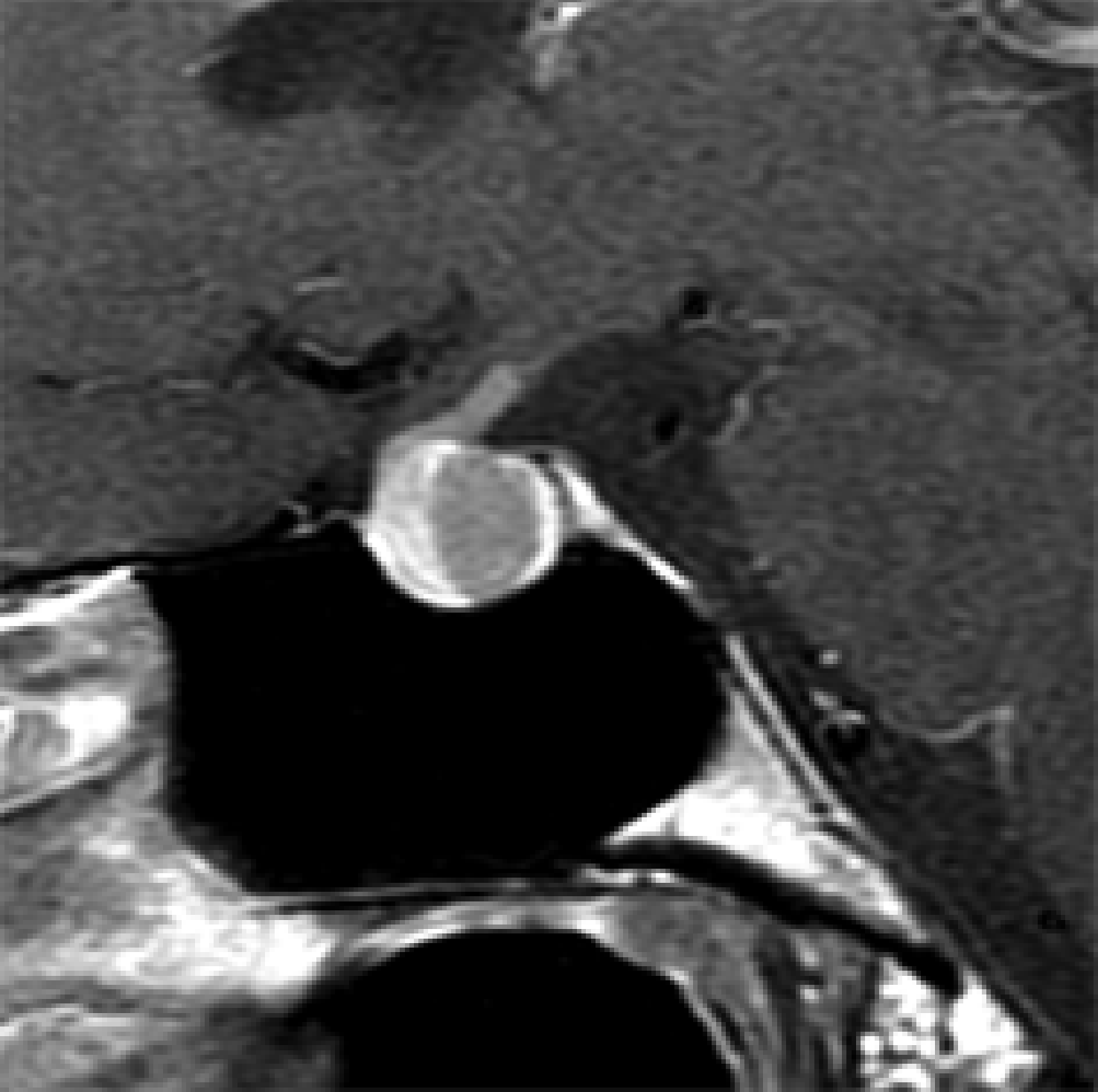

Introduction

Rathke cleft cysts

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Rathke cleft cysts are benign sellar or suprasellar lesions composed typically of a thin cyst wall enclosing a mucous, gelatinous, or caseous liquid core. Excluding adenomas, they are the most common lesion in the sellar region.[1,3] The cysts are a derivative of the Rathke pouch, which itself is a normal component of pituitary development that gives rise to the anterior lobe, pars intermedia, and pars tuberalis of the pituitary gland. Rathke cysts are in effect an inappropriate persistence of a Rathke pouch that fails to close as it normally should early in fetal development. Consequently, the cysts are typically found within the gland or indeed anywhere along the usual migration path of the Rathke pouch. Most Rathke cysts are very often an imaging curio typically uncovered incidentally when imaging is performed for unrelated symptoms or events. The cyst typically appears as a hyperintense MR imaging signal on both T1- and T2-weighted images.[2] Rathke cysts can become symptomatic and cause headaches, hypopituitarism, or visual compromise from compression of the anterior visual pathways. Rarely, they can cause chronic inflammation or infection.

As with most sellar and suprasellar lesions, the preferred treatment (when treatment is indicated for related symptoms) is drainage, decompression, or resection via the transsphenoidal approach. Results have been good with low morbidity. However, many asymptomatic cysts can be safely monitored with serial MR imaging. Additionally, cysts should be monitored even after successful resection since they can recur.[4] This issue of *Neurosurgical Focus* examines contemporary knowledge on the presentation, imaging, treatment, and outcomes of patients with Rathke cleft cysts. *(DOI: 10.3171/2011.5.FOCUS 11116)*

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Neurosurg Focus 31 (1):E1, 2011

Rathke cleft cysts: a review of clinical and surgical management

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The aim of this paper is to provide a comprehensive review of clinical, imaging, and histopathological features, as well as operative and nonoperative management strategies in patients with Rathke cleft cysts (RCCs).

A literature review was performed to identify previous articles that reported surgical and nonsurgical management of RCCs. Rathke cleft cysts are often incidental lesions found in the sellar and suprasellar regions and do not require surgical intervention in the majority of cases. In symptomatic RCCs, the typical clinical presentation includes headache, visual loss, and/or endocrine dysfunction. Visual field testing and endocrine laboratory studies may reveal more subtle deficiencies associated with RCCs. When indicated, the transsphenoidal approach typically offers the least invasive and safest method for treating these lesions. Various surgical strategies including cyst wall resection, intralesional alcohol injection, and sellar floor reconstruction are discussed. Although headache and visual symptoms frequently improve after surgical drainage of RCCs, hypopituitarism and diabetes insipidus are less likely to do so. A subset of more aggressive, atypical RCCs associated with pronounced clinical symptoms and higher recurrence rates is discussed, as well as the possible relationship of these lesions to craniopharyngiomas.

Rathke cleft cysts are typically benign, asymptomatic lesions that can be monitored. In selected patients, transsphenoidal surgery provides excellent rates of improvement in clinical symptoms and long-term cyst resolution. Complete cyst wall resection, intraoperative alcohol cauterization, and sellar floor reconstruction in the absence of a CSF leak are not routinely recommended. *(DOI: 10.3171/2011.5.FOCUS1183)*

Key Words • **Rathke cleft cyst** • **transsphenoidal approach** • **pituitary adenoma** • **endoscopy** • **craniopharyngioma**

Rathke cleft cysts (RCCs) are benign, epithelial-lined cystic remnants of the craniopharyngeal duct that are often discovered incidentally in the sellar or suprasellar region. These lesions remain asymptomatic in the majority of people. According to the findings of one cadaveric study, small RCCs were the most frequently encountered lesions of the sellar area and were noted to be present in 22% of specimens.[34] Despite their relatively high prevalence, however, RCCs are found in only 2%–9% of patients undergoing transsphenoidal operations for symptomatic sellar region lesions.[31,38] Only a small proportion of RCCs exert sufficient mass effect on surrounding structures to result in symptoms and require surgical intervention. The current review focuses on the clinical and operative management of RCCs, including preoperative evaluation and patient selection, intraoperative management, and follow-up care.

Abbreviations used in this paper: DI = diabetes insipidus; RCC = Rathke cleft cyst.

Clinical Presentation and Epidemiology

Symptomatic RCCs typically present during the 4th or 5th decade of life, with a slightly higher female preponderance.[1,4,14,22,23] The typical symptoms associated with RCCs include headache, endocrine dysfunction, and visual loss.[1,4,20,23,26] Visual loss has been reported to develop in 35%–50% of patients undergoing surgical intervention and may include deficits in visual fields as well as in visual acuity.[1,13,14,21,26] Hyperprolactinemia and growth hormone deficiency are relatively common endocrinological findings associated with RCCs, followed by hypocortisolemia and hypogonadism.[1,13] Diabetes insipidus (DI) has been reported as a presenting feature in approximately 7%–20% of patients with RCCs.[13,23] In rare cases, RCCs may present with chemical meningitis, sellar abscess, lymphocytic hypophysitis, or intracystic hemorrhage.[23,32] The term "Rathke cleft cyst apoplexy" has recently been described for cases with sudden-onset symptoms and imaging evidence of intracystic hemorrhage.[9]

Although infrequent, RCCs occasionally cause symptoms in children, potentially resulting in somatic or sexual retardation in addition to the more common symptoms related to mass effect described above.[37]

Preoperative Assessment

All patients with cystic sellar lesions should undergo a comprehensive preoperative evaluation consisting of the appropriate ophthalmological, endocrinological, and neuroimaging studies. A formal visual field examination should be performed in any patient with visual symptoms or evidence of suprasellar cyst extension, as more subtle visual deficits are often detected. A thorough endocrinological history includes screening for symptoms related to fatigue, sexual dysfunction, physical or sexual development, menstrual history, and various hypersecretory endocrinopathies including hyperprolactinemia, Cushing disease, and acromegaly. Laboratory studies should include levels of serum prolactin, free T4, thyroid-stimulating hormone (TSH), morning fasting cortisol, adrenocorticotropic hormone (ACTH), insulin-like growth factor–1 (IGF-1), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in women, and free testosterone in men. Hypothyroidism should be treated prior to considering elective surgical options.

It may be difficult to differentiate other cystic sellar or suprasellar masses from RCCs based on a patient's history, laboratory values, and neuroimaging studies.[10,39] Additional lesions that may be confused with RCCs include cystic craniopharyngiomas, arachnoid cysts, cystic pituitary adenomas, epidermoid tumors, sellar abscesses, and even intrasellar aneurysms. A general guideline is that a serum prolactin level greater than 200 ng/ml is typically consistent with a prolactinoma rather than hyperprolactinemia due to pituitary stalk compression, although this rule may not be as useful for smaller lesions measuring less than 10 mm in diameter. Selection of the appropriate neuroimaging studies including CT scanning, MR imaging, and CT/MR angiography may help differentiate the various cystic sellar lesions.

Imaging Features of RCCs

Magnetic resonance imaging remains the preferred modality for preoperative assessment of RCCs and for differentiating RCCs from other cystic sellar lesions.[39] On MR images, RCCs often appear as well-circumscribed, centrally located spherical or ovoid lesions of the sellar region (Fig. 1). The majority are intrasellar or intra- and suprasellar, although purely suprasellar lesions may occur in a minority of patients (Fig. 2).[3,36] The majority of RCCs are unilobar with a diameter ranging between 5 and 40 mm (mean ~ 17 mm).[23,29,33] They are often identified as having an epicenter located between the anterior and posterior pituitary gland in the region of the pars intermedia. The normal pituitary gland may be displaced in any direction by an RCC, including circumferential splaying if the cyst arises in and remains encased within the gland.[6,30] In the majority of cases, administration of Gd contrast demonstrates little or no enhancement of the cyst wall

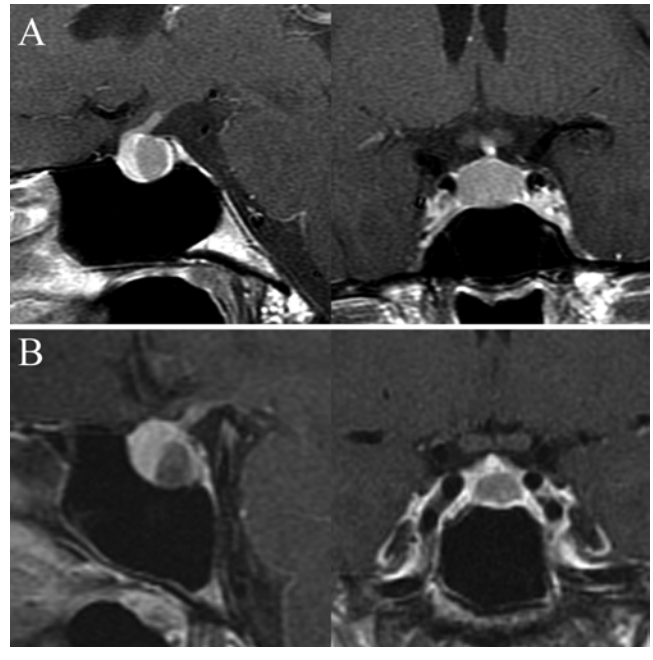

Fig. 1. Sagittal **(left)** and coronal **(right)** Gd-enhanced MR images obtained in 2 patients **(A and B)** with typical intrasellar RCCs. The epicenter of the cyst is in the pars intermedia, and the anterior and posterior pituitary glands are splayed by the cyst. Mild enhancement of the infundibulum is noted.

or contents on MR imaging,[4,5,7] although a thin enhancing rim has been attributed to inflammation or squamous metaplasia of the cyst wall, or to a circumferential rim of displaced pituitary gland.[6,23] The signal intensity of cyst contents on MR images demonstrates high variability on T1 and T2 sequences and has been reported to correlate with the nature of the cystic contents.[2,19,35] Although most RCCs display a homogeneous signal intensity, up to 40% contain a waxy intracystic nodule composed of protein and cellular debris that typically does not enhance following contrast administration.[5–7]

Histopathology

The gold standard for establishing a diagnosis of RCC is histopathological analysis. At times, especially following drainage of an RCC, it may be difficult to obtain a surgical specimen of the cyst wall, occasionally resulting in an inability to obtain a conclusive histological diagnosis. On routine H & E analysis, RCCs typically demonstrate simple columnar or cuboidal epithelium, often with ciliated or mucinous goblet cells (Fig. 3).[11] Pseudostratified columnar cells are also commonly observed. Squamous metaplasia of RCCs has been noted to occur in 9%–39% of patients and is associated with higher rates of cyst recurrence.[1,23,25] Similarly, stratified squamous epithelium occurs in a minority of RCCs and is thought to pose a higher risk for cyst recurrence.[23]

Clinical Management

A majority of patients with RCCs that are discovered incidentally will remain asymptomatic. These lesions do

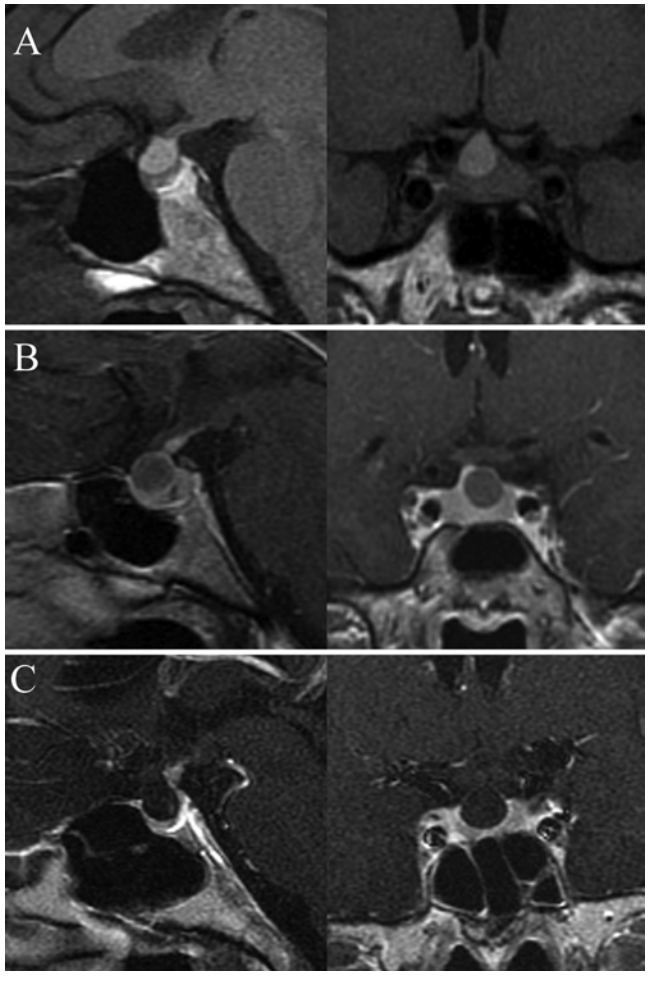

Fig. 2. Sagittal **(left)** and coronal **(right)** Gd-enhanced MR images obtained in 3 patients **(A, B, and C)** with typical supra- and intrasellar RCCs. The epicenter of the cyst is near the infundibulum, and the pituitary gland is displaced inferiorly.

not require surgical management and can be monitored using serial imaging studies.[1] Asymptomatic patients with small RCCs (diameter < 10 mm), normal visual field examination findings, and no evidence of endocrinopathy can be monitored with yearly MR imaging studies or perhaps even clinically if the initial cyst is small and the patient remains asymptomatic. In appropriate patients in whom progressive symptoms that are directly referable to RCCs develop and in those with visual field deficits or underlying laboratory evidence of endocrinopathy, surgical drainage of RCCs remains the preferred treatment option. As an alternative, nonsurgical option for selected asymptomatic patients with larger RCCs (diameter ≥ 10 mm) or those with suprasellar extension, yearly follow-up with MR imaging studies and formal visual examinations may be used to rule out cyst growth or progressive optic apparatus compression and guide surgical decision-making.

Intraoperative Management of RCCs

The transnasal transsphenoidal approach has become the most common surgical approach for treating RCCs. In

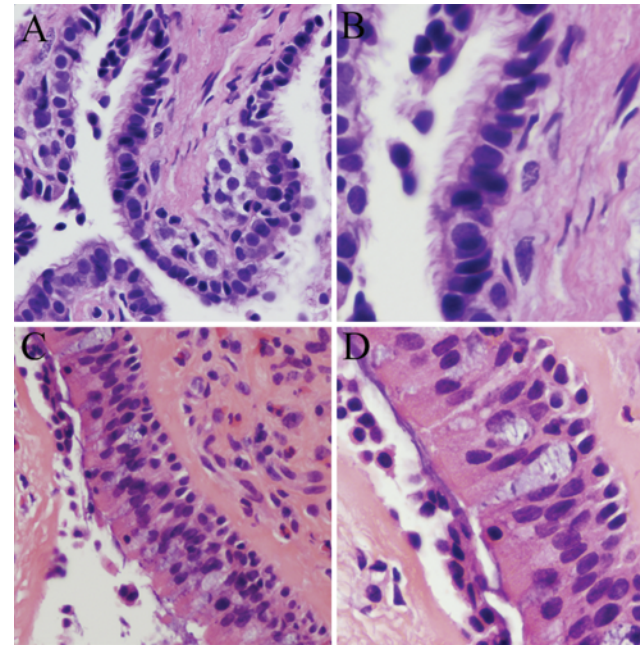

Fig. 3. A and B: Photomicrographs of a typical RCC lined by a single layer of columnar, ciliated epithelium. **C and D:** Photomicrographs of an atypical RCC lined by a thickened columnar epithelium with frequent goblet cells and mucin production. H & E, original magnification × 100 **(A and B)** and × 400 **(C and D)**.

the last 15 years, endoscopic endonasal approaches have become widely used in the surgical management of these lesions.[8,16,27] Although quite rare, open craniotomy may be required in complex cases of giant or purely suprasellar RCCs or in patients in whom a transsphenoidal approach is contraindicated. For most patients, however, extended endonasal approaches have obviated the requirement for craniotomy in all but the most complex RCCs. The benefits of the transsphenoidal approach for treating sellar and suprasellar lesions have been described elsewhere in detail. Routine corticosteroid administration is not necessary for patients with no laboratory evidence of preoperative hypocortisolemia. Postoperative screening for hypocortisolemia, however, should be performed in these patients.

Once the sellar region has been approached, bony removal of the appropriate extent of the sellar floor and adjacent parasellar skull base proceeds as required. In RCCs isolated to the suprasellar region, a transtuberculum extended approach may be ideal for approaching the cyst and preserving normal gland function.[12,24] Less frequently, large retrosellar and retroclival RCCs may require a transclival approach. Although cyst drainage could theoretically be accomplished via a small bony and dural opening, a wide dural opening is preferable because it is thought to facilitate ongoing cyst drainage and potentially prevent RCC regrowth. Upon opening the cyst capsule, its mucinous contents will often extrude under low pressure, and subsequent drainage can be facilitated with the use of a small suction tip. Obtaining a small piece of the anterior cyst wall for pathological examination early on may be easier than attempting this after drainage, especially for smaller cysts. In RCCs consisting of more fibrous, proteinaceous,

or waxy components, a small round angled curette can be useful for delivering these portions of the cyst contents. For typical RCCs located in the region of the pars intermedia, the surgeon must keep in mind that the posterior pituitary gland lies immediately posterior to the cyst wall, and care must be taken to not damage this portion of the gland. Similarly, complete resection of the cyst wall is not typically recommended, as it has been associated with a higher incidence of postoperative DI.[4] Resection of a small portion of the anterior cyst wall for use as a pathological specimen, followed by wide fenestration of the capsule, is an optimal surgical paradigm for treating RCCs and avoiding damage to the posterior pituitary gland and pituitary stalk. After complete drainage of the cyst, the surgeon should assess for evidence of an intraoperative CSF leak, which can be facilitated by performing a Valsalva maneuver. The use of alcohol cauterization has not been shown to reduce recurrence rates of RCCs and should never be used in the event of an intraoperative CSF leak.[26] Sellar floor reconstruction is not recommended in cases in which a CSF leak is not identified to promote continuous drainage of the cyst. If evidence of intraoperative CSF leakage is identified, it can be repaired with the use of a dural substitute and fibrin glue (for smaller, "weeping" leaks), or with an autologous abdominal fat graft and sellar floor buttress (for larger leaks).[15] The use of a pedicled nasoseptal flap or lumbar drain is not required for the overwhelming majority of these lesions. Similarly, routine nasal packing is not routinely performed.

Clinical Outcomes and Follow-Up Strategies

Previous studies have demonstrated high rates (> 90%) of complete resolution of RCCs following surgical drainage.[1,4,14] Similarly, improved headache and visual function have typically been reported in more than 80% of patients after surgical drainage.[4,23] In 2005, Aho et al.[1] reported the largest surgical series to date of RCCs treated in adults (118 patients), with an initial gross-total resection rate of 97% and a recurrence rate of 18% at 5 years. Although headache, visual symptoms, and hyperprolactinemia frequently improve in patients after surgical treatment of RCCs, panhypopituitarism and DI are less likely to improve, and close postoperative surveillance in conjunction with an endocrinologist is warranted.[1,13,14] The incidence of permanent DI after transsphenoidal drainage of RCCs has been reported in 3%–19% of patients and has been associated with complete cyst wall resection.[1,4,14,23]

A small subset of patients harbor RCCs with more aggressive behavior, and they often present with clinical evidence of panhypopituitarism, DI, progressive visual loss, or symptoms similar to meningitis or hypophysitis. These more aggressive RCCs often demonstrate imaging features including a thickened, enhancing, cyst wall; surrounding edema or inflammation; ossification; or even hemorrhagic features (Fig. 4). It has been suggested that RCCs may occasionally leak their caustic contents, resulting in a progressive cycle of chronic inflammation and cyst wall reactivity, and more pronounced clinical symptoms.[17] Rathke cleft cysts with squamous metaplasia and transitional features (such as squamous epithelial cells) may cause them to resemble cystic craniopharyngiomas on histopathological analysis and imaging studies. It has been suggested that the 2 lesions are varying manifestations of a common epithelial precursor.[18,39] Patients with multiple, often progressive clinical recurrences are often noted to have this subset of atypical RCC. In these patients, an argument can be made for a more definitive, complete cyst wall resection rather than repeated fenestration, even at the risk of developing hypopituitarism and DI that can subsequently be treated medically.

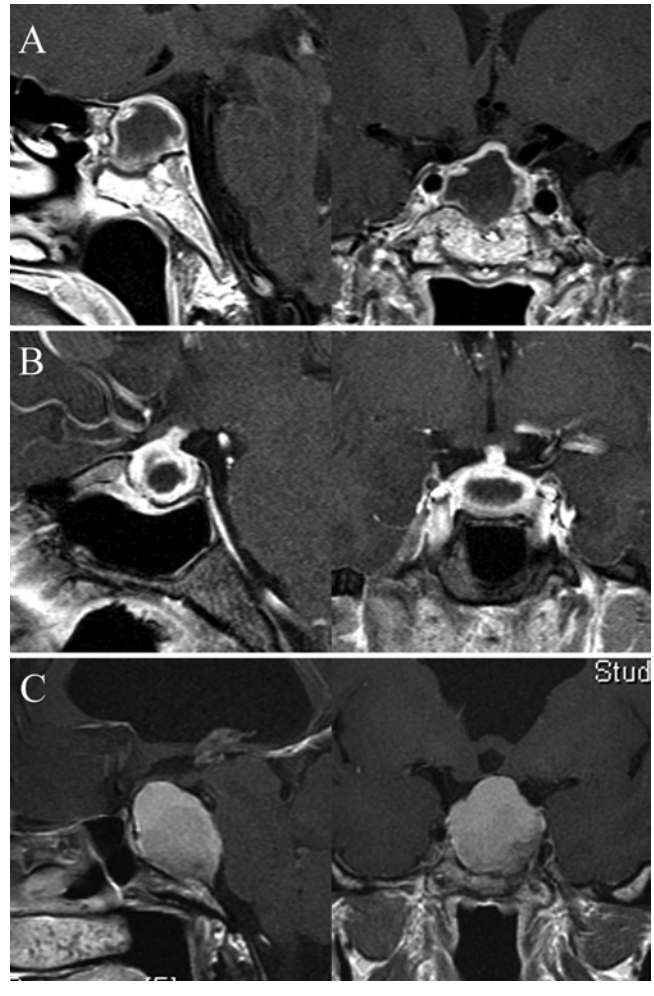

Fig. 4. Sagittal **(left)** and coronal **(right)** Gd-enhanced MR images obtained in 3 patients **(A, B, and C)** with atypical RCCs. **A and B:** A thickened, enhancing cyst wall is visible. Prominent thickening and enhancement of the infundibulum is seen **(B)**. **C:** Severe erosion of the clivus has occurred due to the giant RCC.

Overall long-term recurrence rates after fenestration or resection of RCCs have varied from 3% to 33% and have been reported to correlate with several factors, including the enhancement pattern of the cyst wall on imaging studies, the presence of squamous metaplasia, chronic inflammation or stratified epithelium, the aggressiveness of cyst wall resection, and the insertion of an abdominal fat graft.[1,4,22,23,26,28] After surgical treatment of an RCC, MR imaging is recommended at the 3-month follow-up point and then on a yearly basis for 5 years. After this,

imaging follow-up may be performed every 2–3 years if patients are clinically and endocrinologically stable, with overall follow-up for at least a decade after the operation.

Conclusions

Rathke cleft cysts are benign, epithelial-lined cysts that cause symptoms in a minority of patients in whom they are found. Headache, visual loss, and endocrine dysfunction are the most common presenting features. Transsphenoidal surgery remains the preferred option for patients with symptomatic RCCs or those with subclinical visual loss or hypopituitarism and offers excellent outcomes with regard to symptomatic improvement, preservation of normal pituitary function, and minimization of complications. Recurrence may pose a treatment challenge, especially in a subset of atypical RCCs with chronic inflammation or transitional features such as squamous metaplasia. Close neuroimaging, ophthalmological, and endocrinological follow-up is therefore warranted for up to a decade after resection.

Disclosure

The author reports no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Neurosurg Focus 31 (1):E2, 2011

Symptomatic Rathke cleft cysts: extent of resection and surgical complications

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Object. Rathke cleft cysts (RCCs) are benign masses arising from the embryological Rathke pouch, and are commonly treated by transsphenoidal surgery. The authors retrospectively compared RCC extent of resection—either gross-total resection (GTR) or decompression—to the primary outcome measure, which was recurrences resulting in repeat surgery, and the secondary outcome measure, which was complications.

Methods. Seventy-four patients presenting to the neurosurgical department with RCC were analyzed retrospectively. Sixty-eight patients had a total of 78 surgical procedures, with the diagnosis of RCC confirmed by histological investigation; of these, 61 patients had adequate operative notes for the authors to evaluate extent of resection. Groups were separated into GTR (32 patients) or decompression (subtotal resection or fenestration into the sphenoid sinus; 29 patients) based on operative notes and postoperative imaging. The mean follow-up duration was 60.5 ± 72.1 months (the mean is expressed ± SD throughout).

Results. The average age at the time of the initial surgery was 42.8 ± 17.4 years, and 70% of patients were female. The mean cyst diameter preoperatively was 16.9 ± 17.8 mm. Eight patients had repeat surgery, our primary outcome measure; 3 repeat operations occurred in the GTR group, and 5 in the decompression group. There was no significant difference in recurrence when comparing groups (GTR 9%, decompression 17%; $p = 0.36$). There were no major complications; however, analysis of postoperative minor complications revealed that 11 (34%) GTRs resulted in surgical complications, whereas the decompression cohort accounted for only 3 complications (10%) ($p = 0.03$), with diabetes insipidus (6) and CSF leaks (5) being the most common. Gross-total resection also resulted in an increase in postoperative hyperprolactinemia compared with decompression ($p = 0.03$).

Conclusions. It appears that RCCs require repeat surgery in 13% of cases, and attempted GTR does not appear to reduce the overall rate of recurrence. However, more aggressive resections are associated with more complications in this series. *(DOI: 10.3171/2011.5.FOCUS1175)*

Key Words • **Rathke cleft cyst** • **central nervous system cyst** • **outcome** • **surgical technique**

Rathke cleft cysts (RCCs) are benign sellar cysts, and comprise between 6% and 10% of sellar lesions.[3,6] They are thought to arise from a remnant of the embryological structure, the Rathke pouch, which is typically positioned between the adenohypophysis and the neurohypophysis.[17] Rathke cleft cysts are found frequently at autopsy, and have been reported to occur in 5%–27% of the population.[11–14]

Although RCCs are nonfunctioning, they can result in neurological and endocrine deficits via mass effect on the pituitary axis, optic chiasm, and surrounding anatomy.[6,7,18] As a result, surgical intervention is recommended in symptomatic and at-risk patients, most commonly via a transsphenoidal approach.[1,3,4,10,15] The extent of resection that produces maximum benefit is still somewhat controversial.[1,4,9,16] Theoretically, a more aggressive resection such as a gross-total resection (GTR) would lead to a lower rate of recurrence than a subtotal resection (STR) or fenestration. However, this benefit has not been proven, and GTR conceivably leads to more complications.[1,2,8,15] Furthermore, STR or fenestration techniques are believed to have fewer complications than a more aggressive resection.[10] To date, there has been no conclusive evidence to show whether decompression of RCCs by fenestration or STR can achieve the same level of relief of mass effect as more aggressive approaches, such as a GTR. Similarly, it is also not fully known whether the rate of recurrence is directly correlated with the amount of tumor remaining postoperatively; that is, if a more aggressive resection will ensure a longer tumor-free period. In our study, we aim to answer these questions. We present a case series of patients with RCC in which these two valid paradigms are compared: GTR versus decompression with regard to cyst recurrence and complications due to surgery.

Abbreviations used in this paper: DI = diabetes insipidus; GTR = gross-total resection; PRL = prolactin; RCC = Rathke cleft cyst; STR = subtotal resection; T_4 = thyroxine.

Methods

Inclusion Criteria

The surgical records of 74 patients treated at the Mayo Clinic were obtained from the neurosurgical and pathological data base, in accordance with institutional review board protocol, based on the key word search "Rathke's Cleft Cyst." The patient histories were then reviewed and pertinent information was collected and analyzed. Inclusion criteria for further analyses of recurrence and complications in this study were as follows: 1) pathologically confirmed RCC following surgery at the Mayo Clinic in Rochester, Minnesota and 2) clear documentation of the extent of resection based on operative reports and postoperative imaging. Based on these criteria, 61 patients were included in analyses of recurrence and complications.

Defining Extent of Resection

In the majority of cases, the extent of resection was explicitly stated by the surgeon as a GTR, STR, or fenestration. In all other cases, patients were grouped based on the surgeon's stated impression of the resection. The STR and fenestration groups together compose the decompression cohort.

Recurrence and Complications

Recurrence was defined as radiological evidence of regrowth of the cystic mass postoperatively, found on follow-up imaging examinations, or determined based on associated symptoms. Symptomatic recurrence was defined by repeat operation for symptoms. Likewise, a complication was defined as a new postoperative clinical abnormality related to the surgery.

Statistical Analysis

We used JMP 8.02 (JMP, version 8; SAS Institute, Inc.) to process the data, applying nonparametric statistical tests (Fisher exact test) or the Pearson chi-square analysis where appropriate to assess significance. The Student t-test (Mann-Whitney analysis) was used for groups of 2, and ANOVA for continuous variables for more than 2 groups. Kaplan-Meier survival analysis was used to determine differences in recurrence. The mean is expressed ± SD throughout.

Results

Patient Demographic Data

There was a total of 74 patients presenting with RCC to the neurosurgery department at the Mayo Clinic in Rochester, Minnesota, within the time frame of this study. The mean patient age at the time of the initial treatment was 42.8 ± 17.4 years (range 13–74 years). Fifty-two patients (70%) were female (mean age 42 years), and 22 (30%) were male (mean age 46 years). In 6 patients the RCC was clinically managed, and they never received surgical treatment, whereas the remaining 68 patients underwent a total of 78 surgical procedures. The mean and median follow-up time for surgically treated patients was 60.5 ± 72.1 months and 29.5 months, respectively, based on last clinical contact (Table 1).

TABLE 1: Preoperative demographic data in 74 patients with symptomatic RCCs*

Factor	Total	Extent of Op		p Value
		GTR	Dec	
no. of pts	74	32	29	
age (yrs)	43 ± 17	43 ± 17	48 ± 16	NS
range	13–74	15–71	14–74	
% female	70	72	76	NS
preop size (mm)	17 ± 18	14 ± 8	24 ± 27	NS
range	1–130	1–30	1–130	
preop ant pituitary deficiency†	41%	41%	45%	NS
preop visual deficits	29%	12%	19%	NS
FU (mos)	60 ± 72	78 ± 84	43 ± 56	NS
95% CI (mos)	43–78	47–108	21–65	

* All values are expressed as the mean ± SD. Abbreviations: ant = anterior; Dec = decompression; FU = follow-up; NS = not significant; pts = patients; TSH = thyroid-stimulating hormone.
† Values for this entry indicate number of patients (% of those tested) with elevated PRL, low total T_4, low free T_4, low TSH, or low a.m. cortisol.

Symptoms at Presentation

Of the initial 74 patients in this study, the most common presenting symptoms were headache (57%), lethargy (18%), amenorrhea (15%), diabetes insipidus ([DI] 14%), panhypopituitarism (14%), galactorrhea (12%), impotence (12%), libido changes (11%), dizziness (8%), and oligomenorrhea (8%) (Table 2). Eight of the patients (11%) were diagnosed following incidental detection on workup for other conditions. Formal preoperative visual field perimetry testing demonstrated that 18 (29%) of the 62 patients tested had visual field deficits. Assessment of laboratory values in symptomatic patients who warranted testing revealed that 41% had some preoperative anterior pituitary deficiency, although only 27% presented in this manner.

TABLE 2: Presenting symptoms in 74 patients with RCCs

Presenting Symptom	Frequency (%)
headache	57
visual deficits	29
ant pituitary deficiency	27
lethargy	18
amenorrhea	15
DI	14
panhypopituitarism	14
galactorrhea	12
impotence	12
libido changes	11
dizziness	8
oligomenorrhea	8
seizures	5

Preoperative Imaging

Figure 1 demonstrates a typical appearance of a symptomatic RCC, which were most often hyperintense on T1- and T2-weighted MR images, and isointense on CT scans. Only 1 case was described as calcified. In addition, RCCs were frequently described as cysts with rim enhancement, indicative of either the cyst wall or compressed normal pituitary. The mean size of cysts preoperatively at their maximum diameter was 16.9 ± 17.8 mm. Fifty-seven (77%) of the 74 RCCs were primarily located in the sella turcica, with 4 (5%) of 74 being primarily suprasellar. Thirty-two (43%) of 74 intrasellar cysts had secondary suprasellar extension, with 4 (5%) extending into the hypothalamic area.

Surgical Data

Six (8%) of 74 patients were clinically observed rather than surgically treated, due to lack of severity of symptoms. Sixty (81%), 7 (10%), and 1 (1%) had 1, 2, or 4 surgeries, respectively. Sixty-four (94%) of these 68 patients had transsphenoidal surgery, whereas the others had craniotomies. Sixty-one patients who underwent surgery had clear documentation of the extent of resection by the surgeon. Of these, 32 (52.5%) underwent a GTR. The remainder underwent decompression. Sixteen (26.2%) of 61 procedures were classified as STRs, and 13 (21.3%) as fenestrations.

Primary Outcome: Recurrence

Eleven (18%) of 61 surgically treated patients with RCCs who met the inclusion criteria were found to have a recurrence. Furthermore, 8 (13%) of 61 patients in this population required a repeat operation for symptomatic recurrence. The mean time to recurrence was 6.4 ± 5.8 months for patients who underwent GTR and 9.1 ± 5 months for patients who underwent decompression ($p = 0.4$), with the longest time to recurrence being 180 and 120 months, respectively. There was no significant difference in rate of recurrence or repeat surgery among the different resection groups (7% GTR, 10% STR, 2% fenestration; $p = 0.06$) (Fig. 2). Four repeat operations for recurrences and repairs (50%) were performed in patients who received STR, whereas GTR and fenestration accounted for 3 (38%) and 1 (13%) each, respectively. Also, 4 (25%) of 16 patients undergoing an STR required a second operation, whereas 3 (9%) of 32 and 1 (8%) of 13 with GTR and fenestration, respectively, required a second operation ($p = 0.26$). Comparing GTR to decompression, there were no significant differences in rate of recurrence (13% with GTR vs 24% with decompression; $p = 0.24$) or in rate of repeat operation (9% with GTR vs 17% with decompression; $p = 0.36$) (Table 3). The mean follow-up times for GTR and decompression were 77.5 ± 83.6 months and 43.3 ± 56 months, respectively ($p = 0.07$).

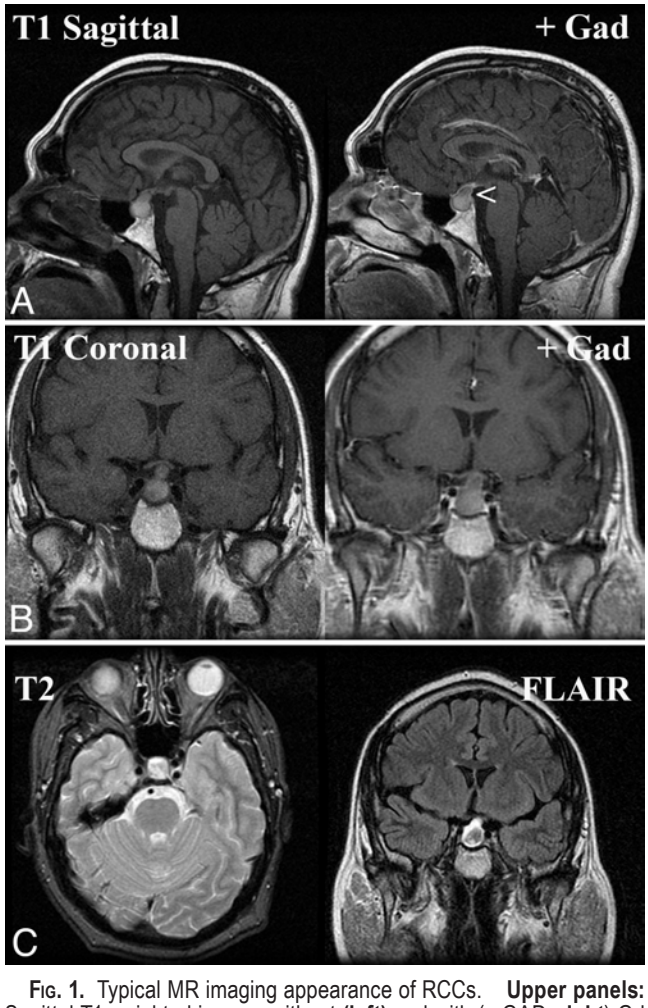

Fig. 1. Typical MR imaging appearance of RCCs. **Upper panels:** Sagittal T1-weighted images without **(left)** and with (+ GAD, **right**) Gd contrast. An *arrowhead* highlights the typical rim contrast enhancement. **Center panels:** Coronal T1-weighted images without **(left)** and with **(right)** Gd contrast. The contrast agent again highlights the rim enhancement. **Lower panels:** Axial T2-weighted MR imaging study **(left)** showing the cyst isodensity to CSF. A coronal FLAIR sequence **(right)** demonstrating again the intrinsic T2 signal within the cyst.

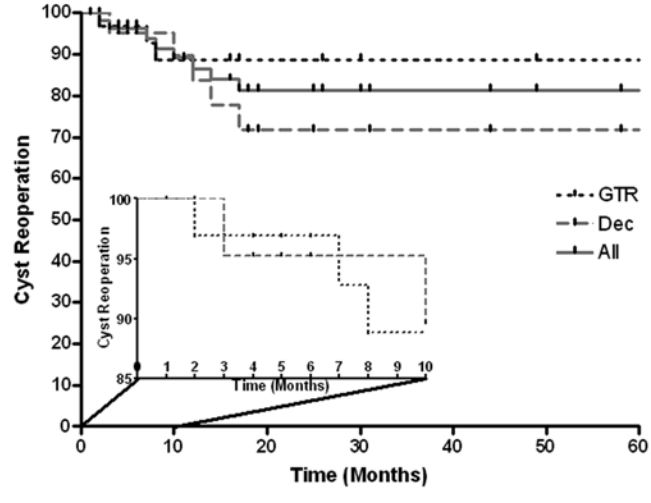

Fig. 2. Kaplan-Meier graph showing time to repeat surgery. The y axis denotes the percentage of patients who have not undergone repeat operation for symptomatic RCC. The **inset** is a magnified view of the first 10 months and a y-axis amplification (85%–100%). All data combined are represented by the *solid gray line* (not present in the magnified view). There was no significant difference in the repeat surgery rate by either Wilcoxon or log-rank analysis. Furthermore, if cases are separated into GTR, STR, and fenestration, there is also no significant difference in repeat operation for symptomatic RCC. Dec = decompression (STR and fenestration combined).

Secondary Outcome: Complications

There were no major complications following surgery. In analyzing these cohorts with respect to minor complications following surgery, 11 (34%) of patients with GTR had complications, and in 3 (10%) of those who underwent decompression the surgery was associated with complications; this difference was significant (p = 0.03). Likewise, 79% of all complications (11 of 14) were associated with GTR. Interestingly, all but one of the complications occurred in females. There was a total of 6 cases of sustained or transient DI postoperatively, 5 of which occurred following GTR. Gross-total resection also was associated with all 5 cases of CSF leaks (p = 0.03), and with the only case of syndrome of inappropriate antidiuretic hormone, whereas decompression was associated with the sole case of postoperative hemorrhage (Table 4).

Visual Field Changes

Eight (47%) of 17 patients with confirmed preoperative visual deficits (for whom a postoperative perimetry study was also available) regained normal vision. The others were either stabilized (6 patients) or showed improvement (3). There were 2 new cases of deficits due to surgery, one each from the GTR and decompression groups.

Pituitary Hormone Data

Preoperative laboratory studies in these patients showed normal mean levels for prolactin (PRL) in females, at 26.5 ± 26.2 ng/ml (range 3.6–130 ng/ml), as well as normal levels for males, at 18 ± 33.6 ng/ml (range 3.3–150 ng/ml); the reference range is 4–30 ng/ml. Fourteen (23.7%) of the 59 patients in whom PRL data were available had hyperprolactinemia preoperatively. Postoperative laboratory studies revealed a decrease in the mean PRL level for females to 23.4 ± 19.3 ng/ml (range 6–79 ng/ml), but an increase for males to 34.1 ± 42.6 ng/ml (range 3.7–109 ng/ml). The mean pre- and postoperative cortisol levels were within the normal reference range (Table 5). Hyperprolactinemia resolved postoperatively in 57.1% of those undergoing GTR and in 100% of those undergoing decompression (not significant). However, there was a significant increase in the rate of new postoperative hyperprolactinemia between groups (GTR 8.3%, decompression 0%; p = 0.03). For patients with low total T_4 or morning cortisol preoperatively, there was no significant difference in the rate of cure, defined as resolution of anterior pituitary axis endocrine abnormality, between GTR and decompression. Likewise, there was no significant difference in the incidence of new abnormalities postoperatively between groups for these hormones (Table 6).

TABLE 3: Postoperative outcome in 61 patients with RCCs

Outcome	Total	Extent of Op		p Value
		GTR (32 pts)	Dec (29 pts)	
radiographic recurrence	18%	13%	24%	NS
symptomatic recurrence w/ reop	13%	9%	17%	NS
postop visual deficits	4%	2%	2%	NS
new postop ant pituitary deficiency*	14%	19%	8%	NS
complications	23%	34%	10%	0.03

* Values indicate number of patients (% of those tested) with elevated PRL, low total T_4, low free T_4, low TSH, or low a.m. cortisol.

TABLE 4: Details of complications overall and by GTR and Dec subgroups*

Complication	Total	Extent of Op		p Value
		GTR (32 pts)	Dec (29 pts)	
overall complications	23% (14)	34% (11)	10% (3)	0.03
DI	10% (6)	16% (5)	3% (1)	NS
CSF leak	8% (5)	16% (5)	0% (0)	0.03
visual worsening	2% (1)	3% (1)	0% (0)	NS
hemorrhage	2% (1)	0% (0)	3% (1)	NS

* Numbers in parentheses represent numbers of patients. The numbers in individual columns will not add up to the total number of complications, because more than one complication may occur in a single patient.

Discussion

Rathke cleft cysts can be treated by GTR, STR, or fenestration—the first and last being the most and least aggressive treatments, respectively. We present a study aimed at examining the most efficacious manner of surgically removing these masses, with regard to both recurrence and surgical complications. We retrospectively analyzed data from patients treated at our institution who received a pathologically confirmed diagnosis of RCC. The patient demographic data are in line with previously reported studies of comparable size; a mean age of 42 years, and 70% of patients were female (range in the literature: 34–41 years, and 52%–79% female).[1,3,8,10,14,15] The primary outcome measure with regard to extent of resection was radiographic and symptomatic recurrence. Secondarily, the rates of surgical complications were assessed. An important difference in this study compared with others with significant numbers of cyst fenestrations is that there were no cases of absolute alcohol instillation into the residual cyst, which has been considered to be an important adjuvant to incompletely resected RCCs.[1,3,8–10,15]

Postoperative Recurrence

Assessing the surgical data available for the 61 patients who met our inclusion criteria, we found that the overall rate of recurrence of 18% was consistent with the existing literature.[1,3,8,10,14,15] In our study, we found no significant difference in the rate of repeat surgery (symptomatic recurrence) among the 3 treatment modalities. It should be noted that STR accounted for 50% of repeat operations, despite accounting for only 25% of the patients. This difference, however, was not significant, but may be related to a poor power (only 61 patients) to detect this difference. To address this, we assessed STR and fenestration together as a cohort of less aggressive surgeries

TABLE 5: Hormone values before and after surgery in patients with RCCs*

Hormone	Female Pts		Male Pts	
	Preop	Postop	Preop	Postop
PRL (ng/ml)	26.5 ± 26.2 (41)	23.4 ± 19.3 (18)	18.0 ± 33.6 (18)	34.1 ± 42.6 (5)
LH (IU/L)	8.1 ± 16.6 (21)	ND	2.8 ± 1.4 (6)	ND
FSH (IU/L)	18.5 ± 36.1 (22)	ND	2.8 ± 1.9 (7)	ND
TSH (mIU/L)	1.5 ± 1.1 (25)	2.2 ± 3.7 (10)	2.2 ± 1.4 (12)	2.6 ± 2.3 (9)
free T_4 (ng/dl)	2.2 ± 2.5 (13)	1.2 ± 0.5 (9)	1.6 ± 1.6 (5)	0.7 ± 0.1 (4)
total T_4 (mg/dl)	6.9 ± 2.4 (28)	12.5 ± 23.9 (18)	5.7 ± 2.2 (15)	5.6 ± 1.9 (10)
a.m. cortisol (mg/dl)	12.4 ± 8.1 (32)	16.3 ± 8.5 (26)	11.8 ± 4.7 (15)	12.5 ± 7.5 (14)
p.m. cortisol (mg/dl)	14.2 ± 17.7 (19)	11.6 ± 9.2 (19)	6.0 ± 4.2 (16)	8.8 ± 6.4 (10)
total testosterone (ng/dl)	NA	NA	302.2 ± 227.3 (12)	312.5 ± 233.4 (10)

* Numbers in parentheses represent the number of patients. Abbreviations: FSH = follicle-stimulating hormone; LH = luteinizing hormone; NA = not applicable; ND = not done.

(decompression) in comparison with GTR. Likewise, we found no significant difference in the rate of either recurrence or repeat operation. This finding is in line with recently published results.[1,3] In a study by Aho et al. looking at outcomes in a large series of patients with RCCs, the authors concluded that there was no difference in rate of recurrence between radical and less radical resections. These groups would be comparable to the GTR and STR/fenestration cohorts presented here. Although the conclusions are similar to our study, the work of Aho et al. included alcohol instillation in their regimen of less radical resection, which confounds direct comparison. There is evidence to suggest that alcohol instillation is not innocuous.[5] Despite this supplementary treatment, the results of the 2 studies are similar, suggesting that the addition of alcohol instillation is not needed. Wait et al.,[15] in an RCC series looking at endocrinopathies in 77 patients, also found that GTR did not lower the rate of recurrence. However, the vast majority of surgeries in that study were GTRs (67 of 77). Our study is unique in contrast to these prior studies because one of them (Aho et al.) is weighted heavily toward fenestration, and the other (Wait et al.) is composed mostly of GTRs, whereas our experience is more evenly divided between more aggressive and less aggressive procedures, and may be more appropriate in answering questions regarding extent of resection.

Postoperative Complications

With regard to complications following surgery, GTR carried a significantly greater overall risk of complications, and this finding has been confirmed by other authors.[1,3] A similar study found that very aggressive treatment resulted in a high rate of postoperative DI (42%) compared with less aggressive treatment modalities (9%) in patients with RCCs.[1] We conducted a very thorough assessment of postoperative complications to elucidate further the difference in outcomes, and found that GTR carried a 16% risk of DI, whereas the risk related to decompression was only 3%. Similarly, CSF leaks were also increased in patients undergoing GTR. Nearly half of the patients with preoperative visual deficits regained normal vision. This is consistent with other studies demonstrating high rates of visual recovery, with low risk of further damage to the chiasm.[1,15]

Pituitary Hormone Deficiency

Pituitary deficiency, in this series, was the third leading symptom at presentation. As was the case in several other studies, 70% of our patient population with RCCs was female, and hyperprolactinemia was often present.[1,10,15] In their study, Wait et al. reported a normalization of PRL levels in symptomatic patients following cyst

TABLE 6: Preoperative and postoperative hormone status of patients with RCCs categorized by GTR and Dec subgroups*

Hormone	Preop Deficiency†		Postop Resolution‡		New Postop Deficiency§	
	GTR	Dec	GTR	Dec	GTR	Dec
PRL	10 (38.5)	4 (16.7)	4 (57.1)	3 (100.0)	3 (8.3)¶	0
total T_4	2 (11.8)	6 (30.0)	1 (50.0)	2 (40.0)	1 (2.9)	0
a.m. cortisol	3 (15.0)	3 (13.6)	2 (100.0)	3 (100.0)	3 (7.1)	1 (2.4)

* Only hormones with substantial pre- and postoperative data are presented.
† Values indicate number of patients (% of those tested) with elevated PRL, low total T_4, or low a.m. cortisol.
‡ Number of patients (%) improved with previously recorded deficiency and available postoperative hormone data.
§ Number of patients (%) without preoperative deficiency noted, and with postoperative data indicating a new deficiency.
¶ Significant at 0.05 level.

resection. Similarly, there was a 70% resolution of hyperprolactinemia following surgery in our series. Although there was no significant difference in the rate of cure between GTR and decompression in this series, we did find that GTR resulted in a significantly increased rate of new postoperative hyperprolactinemia compared with decompression.

Predictors of Recurrence

Although extent of resection does not appear to correlate with an increased risk of recurrence in RCCs, identification of factors that do give insight is warranted. Squamous metaplasia has been reported as one such factor.[1,15] There was 1 case of squamous metaplasia noted, which was in the only patient requiring 4 surgeries. Consistent with previous recommendations to follow these lesions by MR imaging yearly for 10 years, we found a recurrence at 12 years (although on average they tended to present within 1 year), and this recommendation seems valid. Moreover, we could not determine any factors, including preoperative size of the mass, presenting symptoms, and endocrine or visual deficits that would account for this bias.

Conclusions

Patients with RCCs appear to require repeat surgery in 13% of cases, and attempted GTR does not appear to reduce the overall rate of recurrence. However, more aggressive resections are associated with more complications in this series, namely hyperprolactinemia, DI, and CSF leaks.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Acquisition of data: Higgins, Van Gompel. Analysis and interpretation of data: Higgins, Van Gompel. Drafting the article: all authors. Critically revising the article: all authors. Statistical analysis: Higgins, Van Gompel. Administrative/technical/material support: Meyer. Study supervision: Meyer, Van Gompel, Nippoldt.

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Rathke cleft cysts in pediatric patients: presentation, surgical management, and postoperative outcomes

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Object. Rathke cleft cysts (RCC) are benign sellar lesions most often found in adults, and more infrequently in children. They are generally asymptomatic but sometimes require surgical treatment through a transsphenoidal corridor. The purpose of this study was to compare adult versus pediatric cases of RCC.

Methods. The authors retrospectively reviewed presenting symptoms, MR imaging findings, laboratory study results, and pathological findings in 147 adult and 14 pediatric patients who underwent surgery for treatment of RCCs at the University of Californial at San Francisco between 1996 and 2008.

Results. In both the adult and pediatric groups, most patients were female (78% of adults, 79% of pediatric patients, p = 0.9). Headache was the most common symptom in both groups (reported by 50% of pediatric patients and 33% of adults, p = 0.2). Preoperative hypopituitarism occurred in 41% of adults and 45% of pediatric patients (p = 0.8). Growth delay, a uniquely pediatric finding, was a presenting sign in 29% of pediatric patients. Visual complaints were a presenting symptom in 16% of adult and 7% of pediatric patients (p = 0.4). There was no difference between median cyst size in adults versus pediatric patients (1.2 cm in both, p = 0.7). Temporary or permanent postoperative diabetes insipidus occurred in 12% of adults and 21% of pediatric patients (p = 0.4). Kaplan-Meier analysis revealed an 8% RCC recurrence rate at 2 years for each group (p = 0.5).

Conclusions. The incidence of RCCs is much lower in the pediatric population; however, symptoms, imaging findings, and outcomes are similar, suggesting that pediatric RCCs arise from growth of remnants of the embryonic Rathke pouch earlier in life than adult RCCs but do not differ in any other way. It is important to consider RCCs in the differential diagnosis when pediatric patients present with visual impairment, unexplained headache, or hypopituitarism including growth delay. Although the average RCC size was similar in our pediatric and adult patient groups, the smaller size of the pituitary gland in pediatric patients suggests an increased relative RCC size.
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Key Words • pediatric surgery • Rathke cleft cyst • pituitary lesion • transsphenoidal approach

Rathke cleft cysts are nonneoplastic cystic lesions containing mucoid material in the sellar region.[3,30] Rathke cleft cysts (RCCs) and craniopharyngiomas both form from the remnants of the embryonic Rathke pouch,[3,30] which normally reduces to a narrow cleft by the 6th week of embryonic life.[30] The two types of lesions are closely related and may represent a continuum from the simpler RCCs to the more complex craniopharyngiomas.[14] One difference is that RCCs are rare in children (Table 1), while craniopharyngiomas, particularly the adamantinomatous variety, are much more common in children and represent 10% of all pediatric brain tumors.[31] Although the prevalence of RCCs in adults is rather high, with RCCs found in 11%–22% of autopsies,[26,28] most lesions are asymptomatic.[23] The prevalence of RCCs in children, as determined by autopsy and MR imaging studies done for other reasons, is considerably less than in adults, and the asymptomatic RCCs that are identified in children are typically smaller than those found in adults. An autopsy study of 44 children under the age of 9 years, found all RCCs to be smaller than 2 mm.[28] In another study,[27] asymptomatic cystic pituitary lesions were discovered on MR images in 1.2% of 341 patients younger than 15 years of age.

Adults with symptomatic RCCs may present with vi-

Abbreviations used in this paper: GH = growth hormone; IGF-I = insulin-like growth factor–I; RCC = Rathke cleft cyst.

TABLE 1: Summary of prior reports of RCCs in pediatric patients*

Authors & Year	No. of Ped Pts	% Female	Pt Age (yrs) Med	Pt Age (yrs) Range	% w/ HA	% w/ Vis Dysfx	% w/ Incidental Finding	% w/ Preop Hypopit	Cyst Size (cm) Med	Cyst Size (cm) Range	Treatment	Med FU (mos)	% Recurrence
Lim & Yang, 2010	44	50	10.1	0.1–18.2	65	19	30	61	NR	NR	65.9% conservative, 34.1% surgical	15.6	NR
Katavetin et al., 2010	13	85	14	7–17	85	15	0	15	1.22	0.7–1.5	69% conservative, 31% TSS	21.	25 (1 of 4 surgical cases)
Evliyaoglu et al., 2010	1	100	7	NA	0	0	0	100	0.67	NA	microsurgery	24	0
Locatelli et al., 2010	4	NR	10.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Frazier et al., 2008	1	100	14	NA	100	0	0	0	3	NA	TSS	8	0
Takanashi et al., 2005	4	25	2	1–4	0	0	100	0	0.56	0.4–0.85	none	NR	NA
Kim et al., 2004	1	100	11	NA	100	100	0	0	1.6	NA	TSS	4	100
Im et al., 2003	1	100	12	NA	100	100	0	100	1.6	NA	TSS	26	0
Israel et al., 2000	1	100	13	NA	0	100	0	0	1.5	NA	rt craniotomy	5	100
Setian et al., 1999	1	0	8	NA	0	0	0	100	1	NA	TSS	NR	NR
Christophe et al., 1993	7	29	4.29	0.5–13	29	0	43	14.28	1.4	0.8–2.0†	71% observation, 29% TSS	24†	0†
Voelker et al., 1991	1	100	15	NA	100	0	0	100	NR	NA	rt frontal craniotomy	84	0
Towbin et al., 1987	1	0	10	NA	100	0	0	100	NR	NA	NR	NR	NR

* FU = follow-up; HA = headache; Hypopit = hypopituitarism; Med = median; NA = not applicable; NR = not recorded; Ped = pediatric; Pt = patient; TSS = transphenoidal surgery; Vis Dysfx = Visual Dysfunction.

† In the 2 transphenoidal surgery cases.

sual loss, headaches, or endocrinopathy due to the mass effect of the cyst on adjacent structures such as the optic apparatus, dura mater, or pituitary gland, respectively.[23] Although there are copious data describing the manifestations and outcome of RCCs, most are derived from case series of adult patients and little data are available on the presentation or treatment outcomes of RCCs in children. We therefore examined clinical manifestations and outcomes of RCCs in patients 18 years of age or younger who were surgically treated at the University of California at San Francisco and investigated for distinguishing factors in presentation, surgical outcome, and recurrence as compared with our cohort of adult patients who underwent surgery for treatment of RCCs during the same time interval. In particular, since craniopharyngioma, a more aggressive lesion on the opposite end of a continuum of ectodermal derivatives from RCCs, is more common in the pediatric population than in adults, we sought to determine, working within the limitations of the small sample size of pediatric cases of RCC, whether we could identify any examples of more aggressive features in RCCs in children, particularly in terms of cyst size, squamous metaplasia, inflammation, postoperative morbidity such as diabetes insipidus, or RCC recurrence.

Methods

Study Design and Population

We retrospectively reviewed clinical records and imaging studies of 161 patients with RCCs who underwent their first operation at our institution (160 patients) or at another institution followed by recurrence surgically treated at our institution (1 patient) between 1996 and 2008. The patient's age at the time of his or her initial operation was used to represent the age at diagnosis. This study was approved by the University of California at San Francisco Committee on Human Research.

Surgical Technique

The endonasal transsphenoidal microsurgical technique was performed by 3 surgeons (Charles B. Wilson,

44 cases; S.K., 111 cases; and M.K.A., 6 cases) as described elsewhere.[24] A rectangular dural window was created and the edges were coagulated, after which cystic fluid was either expressed spontaneously or an inverted T-shaped incision was made in the pituitary gland to enter the cyst cavity if the gland was anteriorly displaced. For most cysts, further nodular components were removed using suction and ring curettes. In some cases, the visualization of the pituitary fossa was facilitated by the use of a rigid endoscope. In treating patients with RCCs larger than 1 cm in diameter, the resection cavity was packed loosely with an abdominal fat graft, while in those with smaller RCCs the cavity was packed with Gelfoam. Reconstruction of the sellar floor was performed as described elsewhere.[24]

Endocrine Assessment

A preoperative hormonal abnormality was defined as a hormone level outside the normal range for the reporting laboratory. "Postoperative normalization" was defined as a low preoperative level becoming normal postoperatively in a particular hormonal axis. "Postoperative worsening" in pituitary function was defined as any new abnormality in anterior pituitary function, or new need for long-term hormone replacement. Patients were not considered to have worsened function if they transiently required hormone replacement for less than 6 months following surgery (for example, short-term cortisol replacement), but eventually had normal function.

Pathological Review

We reviewed all cases for the pathological confirmation of an RCC diagnosis as evidenced by a nonneoplastic epithelial cyst with well-differentiated cuboidal or columnar epithelial ciliated cells. The pathology reports were further analyzed for changes in the cyst wall such as inflammation or squamous metaplasia.

Statistical Analysis

The Fisher exact test was used to compare categorical variables between the pediatric and adult groups. The Wilcoxon rank-sum test was used to compare continuous variables between the 2 groups. The Kaplan-Meier estimator and log-rank test were used to compare the survival functions of the pediatric and adult groups. Given the exploratory nature of the analyses, p values below 0.05 were considered statistically significant with no correction for multiple testing.

Results

Patient Population

The overall patient cohort was separated into 2 categories based on the patient's age at the time of surgery: 1) an adult group, comprising 147 patients (91%) who were over the age of 18 years at surgery, and 2) a pediatric group, comprising 14 patients (9%) were 18 years or younger at surgery. Of the 147 adult patients, 114 (78%) were female, and 11 (79%) of the pediatric patients were female ($p = 0.9$). The median age of the adult patients was 42 years (range 19–81 years), whereas the pediatric group had a median age of 16 years (range 3–18 years) (Tables 2 and 3).

Presenting Signs and Symptoms

The presenting signs and symptoms in the 2 groups are compared in Table 3. Headaches were a presenting complaint in 48 (33%) of 147 adults and 7 (50%) of 14 children ($p = 0.2$). Twenty-four (16%) of 147 adults and 1 (7%) of 14 children presented with visual symptoms ($p = 0.4$). Two adults (1%) and 1 child (7%) presented with diabetes insipidus ($p = 0.2$). Eleven (7%) of 147 adult and 2 (14%) of 14 pediatric RCCs were found incidentally on imaging ($p = 0.3$).

TABLE 2: Summary of presenting findings in pediatric patients with RCCs in this series*

Case No.	Age (yrs), Sex	HA	Vis Dysfx	Endocrine (preop hypopituitarism)	RCC as Incidental Finding	Cyst Size (diameter in cm)
1	15, F	−	−	+	+	2.0
2	17, M	−	−	−	+	1.5
3	3, F	−	−	−	−	1.3
4	16, F	+	−	−	−	0.7
5	16, F	+	−	−	−	1.1
6	16, M	−	−	+	−	1.9
7	14, M	+	−	−	−	1.0
8	17, F	−	−	+	−	1.0
9	17, F	−	−	−	−	1.5
10	17, F	+	−	+	−	1.1
11	18, F	+	−	−	−	1.5
12	10, F	−	−	+	−	0.9
13	15, F	+	−	−	−	1.5
14	15, F	+	+	−	−	1.1

* − = absent; + = present.

TABLE 3: Comparison of preoperative characteristics in 147 adult and 14 pediatric patients with RCCs*

Characteristic	Total Population	Adults	Ped Pts	p Value
age (yrs)				
median	39	42	16	
range	3–81	19–81	3–18	
female sex	125/161 (78)	114/147 (78)	11/14 (79)	0.9
presenting signs & symptoms				
HA	55/161 (34)	48/147 (33)	7/14 (50)	0.2
growth delay	3/161 (2)	0	3/14 (21)	<0.001
vis dysfx	25/161 (16)	24/147 (16)	1/14 (7)	0.4
symptomatic hyperprolactinemia	24/161 (15)	24/147 (16)	0/14 (0)	0.1
symptomatic hypopituitarism	20/161 (12)	18/147 (12)	2/14 (14)	0.9
RCC as incidental finding	13/161 (8)	11/147 (7)	2/14 (14)	0.3
preop laboratory findings				
hypopituitarism	54/132 (41)	49/121 (40)	5/11 (45)	0.8
hyperprolactinemia	25/161 (16)	24/147 (16)	1/14 (7)	0.7
preop MRI findings				
median RCC diameter ± SD	1.2 ± 0.5 cm	1.2 ± 0.5 cm	1.2 ± 0.4 cm	0.7
high T1 signal intensity†	58/101 (57)	54/93 (58)	4/8 (50)	0.7
preop DI	3/161 (2)	2/147 (1)	1/14 (7)	0.2

* Values represent numbers of patients (%) unless otherwise indicated. p values < 0.05 were considered statistically significant.
Abbreviation: DI = diabetes insipidus.
† Lesions with high signal intensity on T1-weighted MR images were interpreted as cystic fluid with a high protein content.

Preoperative Laboratory Results

Preoperative laboratory studies revealed that 49 (40%) of 121 adults had preoperative hypopituitarism in at least one anterior pituitary hormonal axis, including 4 (36%) of the 11 adults with incidentally found RCCs. These proportions were similar to the 5 (45%) of 11 pediatric patients with preoperative hypopituitarism (p = 0.8), including 1 (50%) of the 2 with incidentally found RCCs. Three of the 14 pediatric patients presented with growth arrest. Of these 3 patients, 2 had low levels of serum GH and IGF-I. Three additional pediatric patients had low levels of serum GH and IGF-I but did not exhibit growth arrest.

Preoperative Imaging

Preoperative MR imaging revealed a median cyst diameter of 1.2 cm in adult patients, identical to that of pediatric patients (p = 0.7). High signal intensity on T1-weighted images, consistent with proteinaceous cyst fluid, was present in 54 (58%) of 93 RCCs in adults and 4 (50%) of 8 RCCs in the pediatric patient group (p = 0.7). Suprasellar extension occurred in 47 (34%) of 138 cysts in adults, compared with 2 (15%) of 13 cysts in pediatric patients (p = 0.2).

Postoperative Endocrine Function

Diabetes insipidus (either temporary or permanent) related to the initial operation occurred postoperatively in 18 (12%) of 147 adults; this rate was comparable to the postoperative occurrence of diabetes insipidus in 3 (21%) of 14 pediatric patients (p = 0.4). Twenty-four (56%) of 43 abnormal axes in adult patients normalized postoperatively, comparable to the 3 (43%) of 7 abnormal axes that normalized postoperatively in the pediatric group (p = 0.6). Thirteen (45%) of 29 adults and 2 (40%) of 5 pediatric patients with low preoperative laboratory values had normalization of at least one axis postoperatively. None of the 3 patients who presented with growth arrest resumed growth postoperatively, and none of the 3 patients who presented with low GH and IGF-I values without growth arrest had normalization of laboratory values postoperatively. Ten (11%) of 93 adults had new postoperative hypopituitarism, comparable to the 1 (10%) of 10 pediatric patients with new postoperative hypopituitarism (p = 0.9). No pediatric patient had new low GH or IGF-I levels postoperatively.

Postoperative Imaging

Rathke cleft cysts that were incompletely resected during the first operation were noted on postoperative MR imaging results. Subtotal resection was noted in 22 (15%) of 147 adults and 2 (14%) of 14 pediatric patients (p = 0.9).

Microbiology

In cases with purulent fluid within the RCC cavity, intraoperative specimens were sent for culturing. Cyst cultures were obtained in 23 (16%) of the 147 adults as compared with 1 (7%) of the 14 pediatric patients (p = 0.7). Culture results were positive for microbial growth in 11 (48%) of the 23 cases involving adults; in the single pediatric case in which purulent fluid was found, culture of the specimen obtained in the first operation was nega-

tive for microbial growth. This specific case led to 2 more operations due to recurrence and specimens were sent for culture each time. The second operation also resulted in a negative culture, with the final operation resulting in a positive culture.

Pathological Features

Inflammation occurred in 17 (12%) of 147 adults and 3 (21%) of 14 pediatric patients ($p = 0.4$), whereas squamous metaplasia occurred in 13 (9%) of 147 adults and 1 (7%) of 14 pediatric patients ($p = 0.9$).

Recurrence Rates

The median duration of radiological follow-up was 23 months in adult patients and 38 months in pediatric patients. The rate of recurrence or postoperative radiological progression was similar in the 2 groups with the adult recurrence rate of 12% (recurrence occurring in 18 of 147 cases) and the pediatric recurrence rate of 14% (2 of 14 cases), yielding Kaplan-Meier estimates of 8% for each group (pediatric and adult) at 2 years ($p = 0.5$).

Discussion

In this study, we compared the presenting symptoms and treatment of RCCs in adults and pediatric patients at our institution over a 12-year period. Although our sample size was small, this likely reflects the rarity of RCCs in children, and our series still represents one of the largest series of pediatric cases of RCC reported to date (Table 1). Moreover, it is the first to compare outcomes in pediatric and adult patients with RCCs treated by the same surgical group during the same study interval, with similar surgical technique being used in both cohorts. Recognizing the limitations of the small sample size due to the rarity of RCCs in children, we did not find significant differences in symptoms, imaging findings, pathological findings, morbidity, or recurrence of RCCs between the adult and pediatric groups.

Although we found no difference in median cyst size between the pediatric and adult groups, when one considers that the normal pituitary height in children 15 years or younger ranges from 0.35 to 0.53 cm compared with the adult pituitary height, which is normally 0.69 cm on average, the cyst size is still relatively larger in the pediatric group.[1,13] Our findings suggest that RCCs in pediatric patients are just a faster growing version of the same benign entity witnessed in the adult population.

In our series, we considered headache to be a symptom, regardless of RCC size—given a recent report in which 90% of patients with headaches and pituitary lesions less than 1 cm in diameter had pain improvement after surgery.[11] While our one patient with headache and a cyst smaller than 1 cm in diameter did not experience postoperative improvement in headache, if we consider headache a symptom of RCC, then 12 of the 14 pediatric patients in our series were symptomatic, with one of the other 2 pediatric patients having laboratory evidence of hypopituitarism, and the other having an incidentally found 1.5-cm RCC with normal endocrine laboratory values but slight mass effect on the overlying optic chiasm on MR imaging. As described earlier, incidentally found RCCs are less common in children than in adults, which likely reflects a combination of the more frequent usage of cranial imaging in adults and the natural history of RCCs, which is slowly progressive—they take time to become radiologically detectable. Our series did not contain any incidentally found RCCs in pediatric patients who were managed with observation (serial imaging) rather than surgery, a few of which have been reported in the literature (Table 1). The largest series of incidentally found RCCs that were managed with observation comprised 115 RCCs in adult patients. The patients were followed up with serial imaging over a mean of 27 months. During this period, 4% of the cysts grew and 22% decreased in size, which led those authors to suggest observing all incidentally found RCCs until evidence of growth, although their series did not correlate the tendency to grow or regress with size at diagnosis.[22] Despite the low morbidity described in operating on RCCs in pediatric patients in our series, until further information is derived correlating the natural history of RCCs with their size at diagnosis, the decision to observe an incidentally found RCC in a pediatric patient with normal laboratory values and no chiasmatic compression is reasonable.

One surgical technique that is rapidly gaining acceptance in the treatment of pituitary lesions is the endoscopic endonasal approach.[5] In the pediatric population, where access through the nares is a challenge, this technique may offer improved visualization.[8,12] This technique, however, is not without its own limitations. In the pediatric population, the small nares can interfere with the introduction of the endoscope unless a concurrent turbinectomy or ethmoidectomy is performed. These procedures increase the likelihood of postoperative rhinological complications, including empty nose syndrome.[6,15] In the future, if access limitations can be overcome, endoscopy may allow for improved visualization of the suprasellar space and medial cavernous sinus.[4] This technique may thus improve the surgeon's ability to identify and address residual disease, an important advantage in cases of hormonally active pituitary tumors where complete removal of all tumor cells is required,[10] but of less concern with an RCC, where cyst drainage and partial wall obliteration is associated with a comparable recurrence rate and less endocrine morbidity than complete wall resection.[2] Given the lack of nasal morbidity and postoperative CSF leak in our series, it is questionable whether an endoscopic approach would confer an advantage in either outcome or morbidity.

Limitations to our study include its retrospective nature and the fact that, while it represents one of the largest surgical series of pediatric RCCs to date (Table 1), the sample size is still small, which limits the ability to definitively identify differences between pediatric and adult RCCs. Given the rarity of pediatric RCCs, a prospective multiinstitutional database of pediatric and adult RCCs would be the best means of confirming our findings in a manner free of these limitations.

Conclusions

We found that the presentation of pediatric patients

with RCCs is similar to that of adults with these lesions—with the exception of delayed growth, which is a uniquely pediatric manifestation—and that the surgical morbidity in pediatric patients was comparable to that seen in adult patients. These findings suggest that surgery should be offered for symptomatic children with RCCs, and is a consideration for incidentally found RCCs whose size suggests a high likelihood of future growth and future symptoms.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Aghi. Acquisition of data: Aghi, Jahangiri. Analysis and interpretation of data: Aghi, Jahangiri. Drafting the article: Aghi, Jahangiri. Critically revising the article: all authors. Statistical analysis: Aghi, Molinaro.

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Rathke cleft cyst presenting with hyponatremia: an unusual presentation

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The authors report a case of Rathke cleft cyst presenting with severe hyponatremia. A 33-year-old man suffered sudden severe headaches, visual changes, dizziness, nausea, vomiting, and a metallic taste in his mouth. Initial laboratory values demonstrated severe hyponatremia. Magnetic resonance imaging revealed a cystic lesion with questionable intracystic hemorrhage, concerning for pituitary apoplexy. Transsphenoidal decompression and drainage of the cyst confirmed the diagnosis of Rathke cleft cyst and resolved the symptoms. Postoperative follow-up studies at 6 months demonstrated normal endocrine function and no evidence of a cyst. *(DOI: 10.3171/2011.4.FOCUS1180)*

Key Words • Rathke cleft cyst • hyponatremia • transsphenoidal surgery • pituitary • endocrine dysfunction • intrasellar cyst • pituitary apoplexy

Rathke cleft cysts are benign cystic remnants of the craniopharyngeal duct. They are commonly located in the sellar and suprasellar region.[5,8] First described by Luschka in 1860 as "an epithelial area in the capsule of the human hypophysis resembling oral mucosa," these remnants of the Rathke pouch have been estimated, based on autopsy examinations, to be present in 22% of the population.[8,18] Despite this high prevalence, they remain largely incidental findings, with an increase in recent diagnoses likely resulting from improvements in imaging of the sellar and suprasellar region.[15–17] Occasionally, however, they may become large enough to cause symptoms, and these cysts now comprise 5%–10% of all resected sellar lesions.[16] Presenting symptoms typically include headache, visual disturbances, and pituitary dysfunction. Endocrinopathies associated with pituitary dysfunction include growth hormone deficiency, hypogonadism, hypothyroidism, and hypocortisolemia.[1]

Rarely, RCCs can present in apoplexy, with acute-onset headache, vision changes or loss, nausea, vomiting, meningismus, and even hypothalamic dysfunction.[3,14] The variation in clinical and imaging appearance and the fact that RCCs can present with nonhemorrhagic apoplexy make diagnosis of this presentation difficult. We report a case of an RCC in which the patient had profound hyponatremia and for whom we had preoperative concern for pituitary apoplexy, an unusual presentation.

Abbreviation used in this paper: RCC = Rathke cleft cyst.

Case Report

History and Presentation. This 33-year-old man without a significant medical history was initially seen at an outside hospital after a motor vehicle accident. At that time, he was thought to have a possible cervical spine injury, for which he was started on a hydrocortisone taper. In addition, he was scheduled for MR imaging the following week. Although he initially had improvement in his symptoms, 5 days later he experienced an acute-onset headache, which progressively worsened over the next 2 days, along with dizziness, nausea, vomiting, and a metallic taste, and he returned to the outside hospital for evaluation. Physical examination showed bitemporal hemianopsia, and laboratory results at that time revealed severe hyponatremia (Na 112 mmol/L). Treatment with 3% hypertonic saline was initiated. Magnetic resonance imaging revealed a 1.3-cm cystic, enhancing intrasellar lesion compressing the optic chiasm superiorly (Fig. 1). Given the acute onset of symptoms and presence of hyponatremia, there was concern for pituitary apoplexy, and the patient was transferred to our facility.

Examination and Operation. On admission to our facility, the patient underwent full endocrinological examination. The levels of follicle-stimulating hormone, luteinizing hormone, and growth hormone were normal, but adrenocorticotropic hormone, cortisol, thyroid-stimulating hormone, and T4 levels were low (Table 1). As the

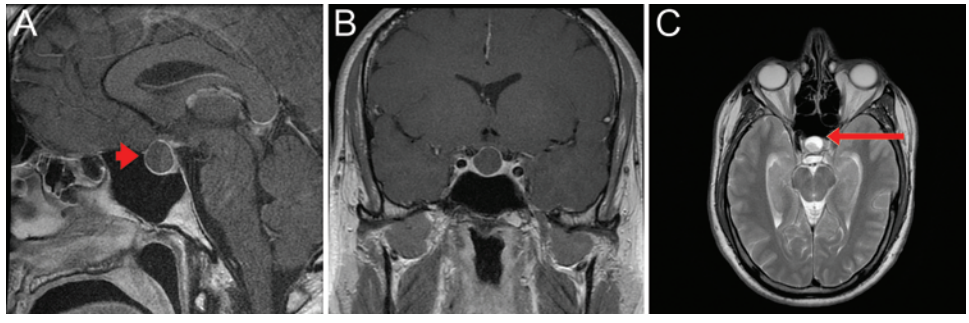

Fig. 1. Initial MR images. Contrast-enhanced sagittal **(A)** and coronal **(B)** T1-weighted MR images showing an intrasellar lesion. Note the rim enhancement and superior displacement of optic chiasm. The lesion has both hypointense *(arrowhead)* and isointense (intracystic nodule) components. Axial T2-weighted MR image **(C)** demonstrating hyperintensity *(arrow)* with isointense component and a questionable fluid level.

patient appeared to be euvolemic and had normal kidney function (blood urea nitrogen level 14 mg/dl and creatine level 0.75 mg/dl), he was not thought to have cerebral salt-wasting syndrome. Because sick euthyroid syndrome was a possibility, the patient was given levothyroxine, and hydrocortisone treatment was restarted. After his endocrinological levels were optimized, the patient was taken to the operating room for decompression and drainage of the cystic mass. A portion of the cyst wall was taken for histological confirmation, and the pathological analysis was consistent with RCC (Fig. 2).

Postoperative Course. The patient's symptoms resolved, and his sodium levels normalized. He was discharged home on postoperative Day 4. At his 6-month follow-up examination, he remained neurologically intact, and follow-up MR imaging revealed complete resolution of the lesion (Fig. 3). In addition, given his normalized endocrine function, the levothyroxine treatment was discontinued, and the hydrocortisone was tapered off as well.

Discussion

Despite the relatively high prevalence of RCC seen on postmortem analysis, these lesions are largely asymptomatic. Patients with symptomatic RCCs commonly present with headaches and symptoms related to the compression of the optic chiasm, hypothalamus, pituitary gland, and structures within the cavernous sinus.[4,10,12,17] Ophthalmological symptoms include vision loss and various visual field defects. Concerning endocrinopathies, deficiencies in growth hormone, hypogonadism, hypothyroidism, and hypocortisolemia have been noted (Table 2).[1,7,9] Hyponatremia is a rarely documented presentation of RCC.[2,6,13]

Our case is similar to the recently reported presentation of nonhemorrhagic RCC apoplexy by Binning et al.;[3] unique to the patient in the current case, however, is that he presented with severe hyponatremia. Previous reports of RCCs presenting with apoplexy all described intracystic hemorrhage seen at the time of surgery.[11,12] In the case series by Binning et al., preoperative MR imaging also demonstrated mixed signal intensities suggestive of hemorrhagic pituitary tumor, which intraoperatively was found to be the intracystic nodule of the RCC. Because intracystic hemorrhages have also been noted within RCCs, the diagnosis becomes even more difficult. Our patient also presented with acute clinical symptoms of apoplexy with preoperative MR imaging findings suggestive of a possible hemorrhagic pituitary tumor. Intraoperatively, we discovered a nonhemorrhagic, cystic lesion consistent with an

TABLE 1: Serum levels of electrolytes and endocrine hormones at admission

Hormone	Patient's Values	Normal Range
Na (mmol/L)	121	136–144
adrenocorticotropic hormone (pg/ml)	2	7–69
cortisol (μg/dl)	1.5	0–9
follicle-stimulating hormone (IU/L)	3.8	1.5–12.4
growth hormone (ng/ml)	0.08	0.01–1
luteinizing hormone (IU/L)	5.2	1.7–8.6
prolactin (mg/ml)	6.6	2.1–17.7
thyroid-stimulating hormone (mU/L)	0.21	0.3–4.0
thyroxine (μg/dl)	4.83	5.1–14.1

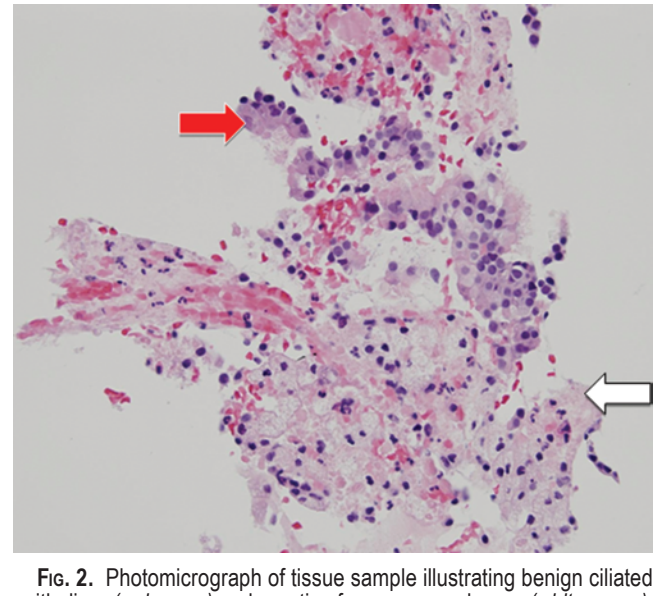

Fig. 2. Photomicrograph of tissue sample illustrating benign ciliated epithelium *(red arrow)* and reactive foamy macrophages *(white arrow)*. H & E, original magnification × 400.

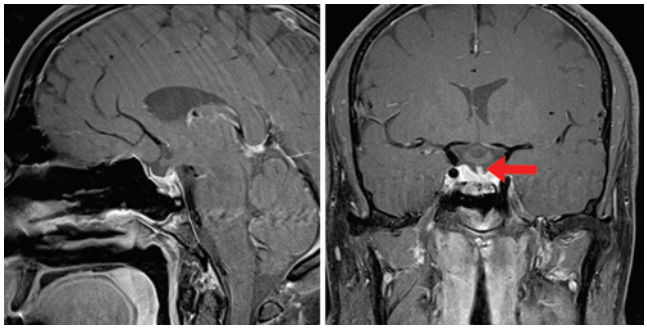

Fig. 3. Follow-up T1-weighted contrast-enhanced sagittal **(left)** and coronal **(right)** MR images showing interval removal of heterogeneous lesion and return of pituitary stalk to its original location *(red arrow)*.

RCC. The cause of the hyponatremia presents an interesting clinical quandary. There have been 10 reported cases of hyponatremia as the presenting symptom in RCC.[2,6,13] In a retrospective analysis, Ogawa et al.[13] described the largest series. They described 8 patients with an RCC who presented with symptomatic hyponatremia, which was postulated to be due to hypocortisolemia caused by inflammatory damage from the RCC within the anterior pituitary gland. Because our patient was on corticosteroid therapy prior to admission to our hospital, it is difficult to say with certainty whether the RCC caused a transient hypocortisolemic state resulting in hyponatremia. The resolution of our patient's hyponatremia, hypothyroidism, and clinical symptoms shortly after decompression and drainage of the RCC provides evidence that an RCC may present with apoplectic symptoms and acute related endocrinopathies including hyponatremia.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Couldwell. Acquisition of data: Sivakumar. Analysis and interpretation of data: Sivakumar, Cole. Drafting the article: Sivakumar. Critically revising the article: Couldwell, Cole. Study supervision: Couldwell.

TABLE 2: Clinical presentation of RCCs

headache
visual symptoms
decreased/lost vision
visual field defects
hormonal abnormalities
growth hormone deficiency
hypogonadism
hypothyroidism
hypocortisolemia
hyperprolactinemia
panhypopituitarism
apoplexy
hemorrhagic
nonhemorrhagic

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