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 California 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 com-

mon 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	%	Pt Age (yrs)		% w/ HA	% w/ Vis Dysfx	% w/ Incidental Finding	% w/ Preop Hypopit	Cyst Size (cm)		Treatment	Med FU (mos)	% Recurrence
			Med	Range					Med	Range			
Lim & Yang, 2010	44	50	10.1	0.1–18.2	65	19	30	61	NR	NR	65.9% conserva- tive, 34.1% sur- gical	15.6	NR
Katavetin et al., 2010	13	85	14	7–17	85	15	0	15	1.22	0.7–1.5	69% conserva- tive, 31% TSS	21.	25 (1 of 4 surgi- cal 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 craniot- omy	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,

Rathke cleft cysts in pediatric patients

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 $\pm$ SD	1.2 $\pm$ 0.5 cm	1.2 $\pm$ 0.5 cm	1.2 $\pm$ 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-

Rathke cleft cysts in pediatric patients

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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