Suprasellar Rathke Cleft Cysts: Clinical Presentation and Treatment Outcomes

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BACKGROUND: Rathke cleft cysts (RCCs), benign remnants of the Rathke pouch typically arising in the sella, sometimes have suprasellar extension. Purely suprasellar RCCs are rarely reported.

OBJECTIVE: To compare the presentations, surgical outcomes, and pathology of purely suprasellar RCCs and sellar-based RCCs.

METHODS: We retrospectively reviewed records, magnetic resonance images, laboratory results, and pathology of 151 RCC patients surgically managed at our institution from 1989 to 2009. The RCCs were classified as purely sellar (type I, n = 76), sellar with suprasellar extension (type II, n = 56), or purely suprasellar (type III, n = 19).

RESULTS: The RCCs with a suprasellar component (types II and III) more commonly presented with visual dysfunction ($P < .001$). Complete cyst drainage occurred in 89%, 55%, and 38% of type I, II, and III RCCs, respectively ($P < .001$). Vision improved in 100%, 55%, and 33% and headache improved in 74%, 64%, and 29% of type I, II, and III patients, respectively ($P = .02$). Temporary or permanent postoperative diabetes insipidus occurred in 5%, 16%, and 21% of type I, II, and III patients, respectively. ($P < .001$). In a multivariate analysis, RCC type was the only factor predicting recurrence. Kaplan-Meier 3-year recurrence/progression rates were 0%, 16%, and 29% for type I, II, and III RCCs, respectively ($P < .001$, type I vs II, type I vs III; $P = .5$ type II vs III).

CONCLUSION: The RCCs with a suprasellar component are neurosurgically challenging because of their proximity to the optic chiasm and infundibulum. Compared with sellar-based RCCs, RCCs with a suprasellar component more frequently present with visual dysfunction, are more difficult to completely eliminate, recur more frequently, and are associated with higher postoperative endocrine morbidity, and their preoperative visual dysfunction and headache less frequently improve with surgery. These factors must be considered during the treatment of RCCs with a suprasellar component.

KEY WORDS: Pituitary, Rathke cleft cyst, Suprasellar, Transsphenoidal surgery, Visual symptoms

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Rathke cleft cysts (RCCs) are benign lesions that typically arise within the sella between the anterior and posterior lobes of the pituitary.[1] Most often asymptomatic, RCCs have been found incidentally in 4% to 33% of autopsies.[2-5] These lesions, however, can cause mass effect on surrounding structures such as the pituitary gland and optic chiasm, leading to headache, pituitary dysfunction, or visual disturbance.[6-8] Although asymptomatic RCCs can safely be followed up with serial imaging,[6] the standard treatment for symptomatic RCCs is surgical decompression, typically through a transsphenoidal approach. Several large series of symptomatic RCCs have demonstrated good resolution of headache, hormonal dysfunction, and visual disturbances with surgical management with acceptable surgical morbidity.[6,7,9-16]

ABBREVIATION: RCC, Rathke cleft cyst

Rathke cleft cysts are remnants of the Rathke pouch, a structure of ectodermal origin formed during the fourth week of gestation (Figure 1).[1] The Rathke pouch extends caudally to fuse with the infundibulum around the eighth week of gestation, forming the craniopharyngeal duct. The Rathke pouch then leads to the formation of

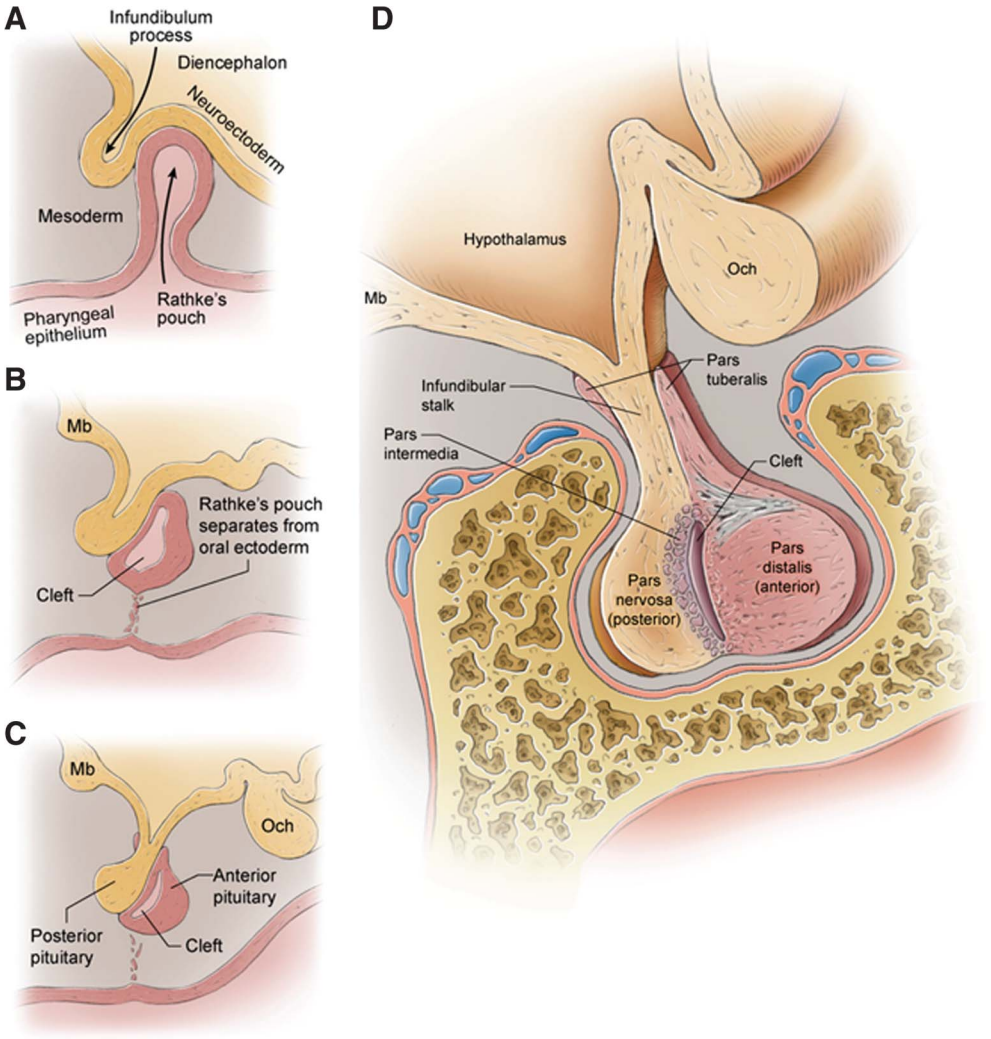

FIGURE 1. *Pituitary gland development.* **A**, *the pituitary gland is derived from 2 sources. The anterior lobe originates from an upgrowth of ectoderm from the roof of the stomodeum (pharyngeal epithelium), whereas the posterior lobe (along with the rest of the diencephalon) originates from a downgrowth of neuroectoderm. In the middle of the fourth week, a diverticulum, the Rathke pouch, begins as a dorsal evagination from the pharyngeal epithelium and then grows upward from the roof of what will become the mouth toward the developing brain. As the upgrowth contacts a ventral evagination or downgrowth from the diencephalon of the brain, the infundibular process, it begins to pinch off from its connection with the stomodeum.* **B**, *by the sixth week, the connection between the Rathke pouch and the oral cavity of the pharyngeal epithelium degenerates, after which (*C*) the cells of the Rathke pouch proliferate to form the pars distalis (also called the anterior pituitary or adenohypophysis), and the infundibular process forms the neurohypophysis (the posterior lobe of the pituitary gland).* **D**, *the cells of the Rathke pouch also extend up the anterior aspect of the infundibulum as the pars tuberalis. The posterior surface of the Rathke pouch does not proliferate but forms the poorly developed pars intermedia. The infundibulum, having grown down from the floor of the diencephalon, expands as the axons of cells in the diencephalon grow down into it. Although the Rathke pouch normally closes early in fetal development, a remnant often persists as a Rathke cleft in the pars intermedia between the anterior and posterior lobes. A Rathke cleft (persistent material from Rathke pouch) can sometimes expand to form a Rathke cleft cyst, which can be found in a purely sellar location centered in the pars intermedia (type I cysts), a sellar location with suprasellar extension (type II cysts), or a purely suprasellar location, likely reflecting origin from persistent suprasellar Rathke pouch cells that gave rise to the pars tuberalis (type III cysts). Mb, mammillary bodies; Och, optic chiasm.*

the adenohypophysis and pars intermedia while the infundibulum generates the neurohypophysis. During this time, the Rathke cleft is formed in the region of the pars intermedia. Failure of this cleft to regress during further development can lead to cystic dilation and the formation of an RCC.[1,6] Larger RCCs can extend upward into the suprasellar region, and comparisons of symptomatic and asymptomatic lesions have suggested that large size and suprasellar extension of RCCs may be associated with a greater tendency toward symptomatic presentation.[9,13] Although most RCCs originate in the sella, there have been reports of purely suprasellar RCCs. To date, these rare entities have been described only in isolated case reports or as a few cases found within larger series of RCCs in which sellar vs suprasellar stratification was not performed,[10,11,13,16-40] and it is not clear how the treatment outcomes of purely suprasellar RCCs compare with those of typical sellar-based RCCs with or without suprasellar extension. We hypothesized that, given the challenges of working near the pituitary stalk and optic chiasm, purely suprasellar RCCs would be more difficult to treat and their treatment would have a higher likelihood of recurrence and higher morbidity compared with typical RCCs based within the sella.

MATERIALS AND METHODS

Study Design and Population

This study was approved by the University of California, San Francisco Committee on Human Research. We retrospectively reviewed records of all 165 consecutive patients with RCCs who underwent their initial operation at our institution from 1989 to 2009. Operations were performed by 3 surgeons (Charles B. Wilson, 27 cases; S.K., 114 cases; and M.K.A., 10 cases). Inclusion criterion was a pathology report consistent with RCC (n = 151). Cases in which the surgeon suspected RCC infection were excluded from this analysis.[41] The 151 patients underwent a total of 173 operations at our institution. Indications for cyst resection included symptomatic cysts, laboratory evidence of hypopituitarism, documented growth, or asymptomatic cysts $>$ 1 cm or in close enough proximity to the optic chiasm to warrant prophylactic treatment. A transsphenoidal corridor was used in all cases and was achieved with a sublabial approach in the initial 27 cases, an endonasal microsurgical approach in 121 subsequent cases, or an endonasal endoscopic approach in 3 cases. All operations involved cyst drainage with partial, not radical, wall excision, and some involved obliteration of the cyst wall by instilling absolute ethanol (n = 118), as described previously,[10,42] or peroxide (n = 4) for 60 seconds. Cyst diameter and imaging characteristics were recorded for all cases in which a preoperative magnetic resonance imaging (MRI) was available (n = 130).

Parameters Assessed

Age at diagnosis was defined as the patient's age at the time of the first operation. All pathology reports were reviewed for pathology confirming the diagnosis of an RCC as evidenced by a nonneoplastic epithelial cyst with well-differentiated columnar or cuboidal epithelial ciliated cells. All pathology reports were also analyzed for alterations in the cyst wall such as squamous metaplasia or inflammation. Preoperative and postoperative anterior and posterior lobe pituitary dysfunction was assessed by noting pituitary hormonal levels and whether patients were on hormone replacement. For purposes of comparison, RCCs were divided into 3 categories based on anatomical location on preoperative MRI: type I, purely sellar RCCs (n = 76); type II, sellar RCCs with suprasellar extension (n = 56); and type III, purely suprasellar RCCs (n = 19; Figure 2).

Follow-up Imaging

Postoperative MRIs were obtained at 6 weeks in 136 patients. The remaining 15 patients (8 type I, 5 type II, and 2 type III) obtained immediate postoperative MRIs before their discharge for financial and scheduling reasons. In terms of further imaging, our standard recommendations were that, if there was no residual cyst, routine follow-up MRIs were scheduled at 6 weeks, 3 months, 6 months, and 1 year; annually thereafter for 5 years; and every 2 years for the next 5 years. If a residual cyst was noted, after the first year of imaging with the above protocol (MRIs at 6 weeks, 3 months, 6 months, and 1 year), repeat MRI was recommended every 6 to 9 months for a total of 5 years and then annually for the next 5 years if there was no change. Actual duration of recorded radiographic follow-up did not always extend as long as these recommendations, with the actual mean duration of follow-up stated in the Results. Indications for repeat resection included symptomatic cyst recurrence. Craniotomy was used on repeat resection if there was evidence of cyst reaching posteriorly toward the third ventricle or superior or posterior to the chiasm.

Statistical Analysis

Analysis of variance was used for parametric comparisons when the dependent variable was continuous, and a χ^2 test was used to compare proportions. Kaplan-Meier analysis was used to assess actuarial radiographic recurrence rates, with time until radiographic recurrence or time until last MRI showing no radiographic recurrence recorded for each patient. Risk factors for recurrence were analyzed with univariate and multivariate Cox regression (SPSS Statistics 17.0 software; SPSS Inc, Chicago, Illinois). Nominal P values are presented with no formal adjustment for multiple comparisons. When testing for differences in demographics, to reduce the risk of false positives, we used a more stringent criterion of significance ($P < .01$) when comparing the 3 cyst types overall and then calculated the P values for comparisons between each of the 3 different pairs of cyst types for a parameter only when the overall P value was $< .01$. For assessing improvement in symptoms, only those presenting with the symptom were included. Because this reduced the available sample size and the power to detect differences, the less stringent criterion of $P < .05$ was used to declare significance for these comparisons. However, interpretation of the data takes into account the increased possibility of false positives that resulted. In considering time to recurrence, our primary hypothesis related to the role of 2 variables (cyst type and size) on recurrence. Therefore, a Bonferroni correction required the use of $P < .03$ to define the significance of the univariate analysis of these 2 variables. In addition, univariate analyses were used to investigate the possible impact of other variables (squamous metaplasia, age, sex, inflammation, use of fat graft, and ethanol irrigation) on cyst recurrence, with no adjustments for multiple comparisons made, given the exploratory nature of those separate analyses. Only variables with $P < .1$ in univariate analyses were investigated in multivariate analyses.

RESULTS

Patient Population and Preoperative Findings

Table 1 lists the population demographics for the overall cohort and each RCC type. Patients with type I RCCs were younger

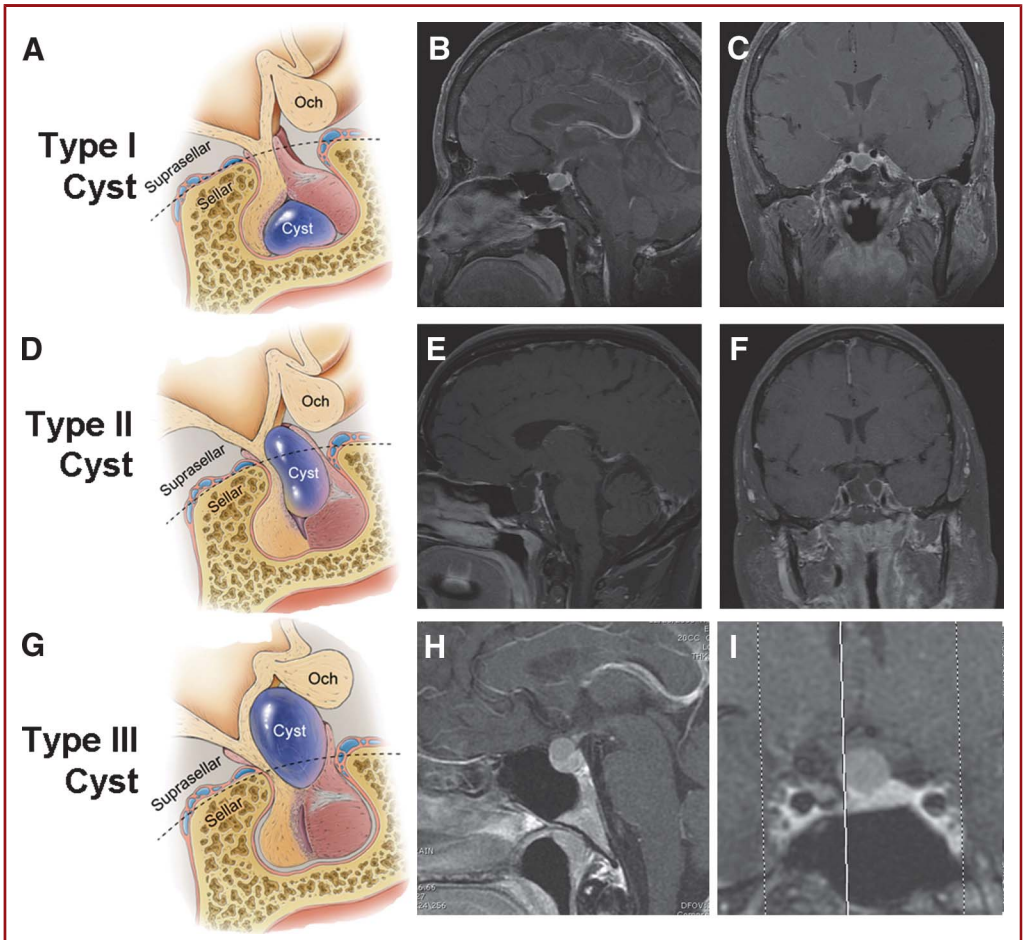

FIGURE 2. *Anatomical subtypes of Rathke cleft cysts (RCCs). Diagram and T1-weighted sagittal and coronal MRIs with contrast for type I (A-C), type II (D-F), and type III (G-I) RCCs. Type I RCCs involve only the sella. Type II RCCs are based in the sella and have suprasellar extension. Type III RCCs are purely suprasellar. Och, optic chiasm.*

(mean age, 34 years) than patients with type II (mean age, 48 years) or type III (mean age, 43 years) RCCs ($P < .001$). Sex did not differ significantly among patients with the different RCC types. The most common presenting symptoms were headache (41%), symptomatic hypopituitarism (32%), and visual dysfunction (13%). Hypopituitarism based on preoperative laboratory studies was found in 32% of patients. Patients with either type II or III RCCs had a significantly higher incidence of preoperative visual dysfunction compared with patients with type I RCCs ($P < .001$). There was also a trend toward a higher incidence of visual dysfunction in type III compared with type II RCCs ($P = .1$). The incidence of headache as a presenting symptom did not vary with cyst type ($P = .2$). Cyst diameter on preoperative MRI averaged 1 cm in type I RCCs, which was less than the 1.5- and 1.7-cm average diameters in type II and III RCCs, respectively ($P < .001$). Preoperative MRI demonstrated a reduction in cyst protein content in type III RCCs compared with sellar-based type I and II RCCs ($P < .001$ and $P = .04$, respectively), with protein content assessed by T1 brightness. Of the 16 type III RCCs in which the location of the pituitary stalk could be definitively ascertained on preoperative MRI, 15 displaced the stalk posteriorly.

Surgical Results

Complete cyst drainage was achieved in 89%, 55%, and 38% of type I, II, and III RCCs, respectively ($P < .001$), leading to a mean postoperative reduction in cyst diameter of 96%, 76%, and 69% ($P < .001$). When the volumetric analysis was limited to incompletely removed cysts, the mean postoperative reduction in cyst diameter was 68%, 59%, and 53% for type I, II, and III cysts, respectively ($P = .7$). Headaches improved in 74% of type I, 64% of type II, and 29% of type III patients ($P = .02$). Of the patients presenting with visual dysfunction, 100% of type I, 55% of type II, and 33% of type III patients had visual improvement postoperatively ($P = .03$). Laboratory hypopituitarism normalized after surgery in any abnormal axis in 60% of patients with type I cysts, 32% of patients with type II cysts, and 50% of patients with type III cysts ($P = .2$).

TABLE 1. Population Demographics[a]

	Total Population	Type I (Sellar)	Type II (Sellar With Suprasellar Extension)	Type III (Purely Suprasellar)	*P*,[b] Overall	*P*,[c] Type I vs II	*P*,[c] Type I vs III	*P*,[c] Type II vs III
Patients, n	151	76	56	19				
Mean (SD) age, y	40 (17)	34 (15)	48 (17)	43 (15)	**<.001**	**<.001**	**.03**	.3
Female, n (%)	119 (79)	59 (78)	46 (82)	13 (68)	.6			
Presentation, n (%)								
Headache	62 (41)	35(46)	20 (36)	7 (37)	.2			
Symptoms suggesting hypopituitarism	48 (32)	29 (34)	15 (25)	4 (21)	.3			
Visual dysfunction	20 (13)	2 (3)	11 (20)	7 (37)	**<.001**	**<.001**	**<.001**	.1
Symptomatic hyperprolactinemia	14 (9)	10 (13)	4 (7)	0 (0)	.08			
Incidental	23 (15)	7 (9)	13 (23)	3 (16)	.04			
Laboratory hypopituitarism	48 (32)	16 (21)	25 (45)	7 (37)	**.009**	**.004**	.2	.6
Laboratory hyperprolactinemia	24/108 (22)	13/50 (26)	9/47 (19)	2/11 (18)	.3			
Preoperative MRI characteristics								
Mean (SD) RCC diameter, cm	1.3 (0.5)	1 (0.3)	1.5 (0.5)	1.7 (0.6)	**<.001**	**<.001**	**<.001**	.8
T1 dark (%)[d]	28 (19)	11 (15)	11 (20)	6 (32)	.08			
T1 bright (%)[e]	100 (67)	61 (81)	33 (59)	6 (32)	**<.001**	**.005**	**<.001**	**.04**

[a]RCC, Rathke cleft cyst.
[b]Comparing the 3 RCC types.
[c]Comparison between different RCC types was performed for cases in which *P* (overall) was <.01 (bold); specific subtype comparisons were considered significant if $P < .05$ (bold).
[d]T1 dark lesions interpreted as cystic fluid with low protein content.
[e]T1 bright lesions interpreted as cystic fluid with high protein content.

Pathological Features

In cases when the cyst wall was sampled, inflammation occurred in 9 of 75 (12%) of type I, 8 of 57 (14%) of type II, and 4 of 18 (22%) of type III RCCs ($P = .3$). Squamous metaplasia occurred in 4 of 75 (5%) of type I, 6 of 57 (11%) of type II, and 3 of 18 (17%) of type III RCCs ($P = .02$).

Surgical Morbidity

Postoperative diabetes insipidus of a temporary or permanent nature occurred in 5% of type I, 16% of type II, and 21% of type III patients ($P < .001$). New and permanent diabetes insipidus occurred in only 1 type II patient, whereas 1 type III patient with preoperative diabetes insipidus also had permanent postoperative diabetes insipidus. A postoperative cerebrospinal fluid leak requiring surgical repair occurred in 3 patients, all of whom had type II RCCs.

Recurrence Rates

The mean duration of follow-up was 30 months (range, 1-163 months) in all patients and 29 months (range, 2-106 months) in the 144 patients who did not experience radiographic recurrence or progression. Radiographic recurrence or progression was observed in 3% of type I, 18% of type II, and 26% of type III RCCs (Figures 3 and 4). Kaplan-Meier actuarial 3-year recurrence/progression rates were 0% for type I, 16% for type II, and 29% for type III RCCs (Figure 5). One of 2 type I RCCs (50%), 7 of 10 type II RCCs (70%), and 4 of 5 type III RCCs (80%) that recurred underwent reoperation ($P = .09$). Two type II patients and 1 type III patient underwent a craniotomy for cyst recurrence. The remaining patients underwent repeat transsphenoidal resections. In univariate analyses investigating the effect of 2 primary variables, cyst type and size, on RCC recurrence, cysts with a suprasellar component had greater recurrence ($P < .001$, type III and II combined vs type I; Table 2), whereas increased cyst diameter did not increase RCC recurrence ($P = .06$; Table 2). Additional analyses found that none of the 6 exploratory secondary variables (metaplasia, age, sex, inflammation, use of fat graft, and use of intraoperative ethanol irrigation) increased RCC recurrence in univariate analyses. In a multivariate analysis involving cyst size and type, cysts with a suprasellar component had greater recurrence ($P = .004$, type III and II combined vs type I; Table 2).

DISCUSSION

Rathke cleft cysts are thought to be nonobliterated remnants of the primitive craniopharyngeal duct, which is a part of the Rathke pouch. In the superoinferior plane, RCCs are usually located entirely within the sella or contain both intrasellar and suprasellar components. In the anteroposterior plane, RCCs typically reside between the pars anterior and pars intermedia of the pituitary gland. Purely suprasellar RCCs situated above a normal sella are rare. The Rathke pouch gives rise to the pars distalis (anterior lobe) and pars intermedia (intermediate lobe) in the sella, as well as the pars tuberalis, a structure that resides above the anterior lobe and

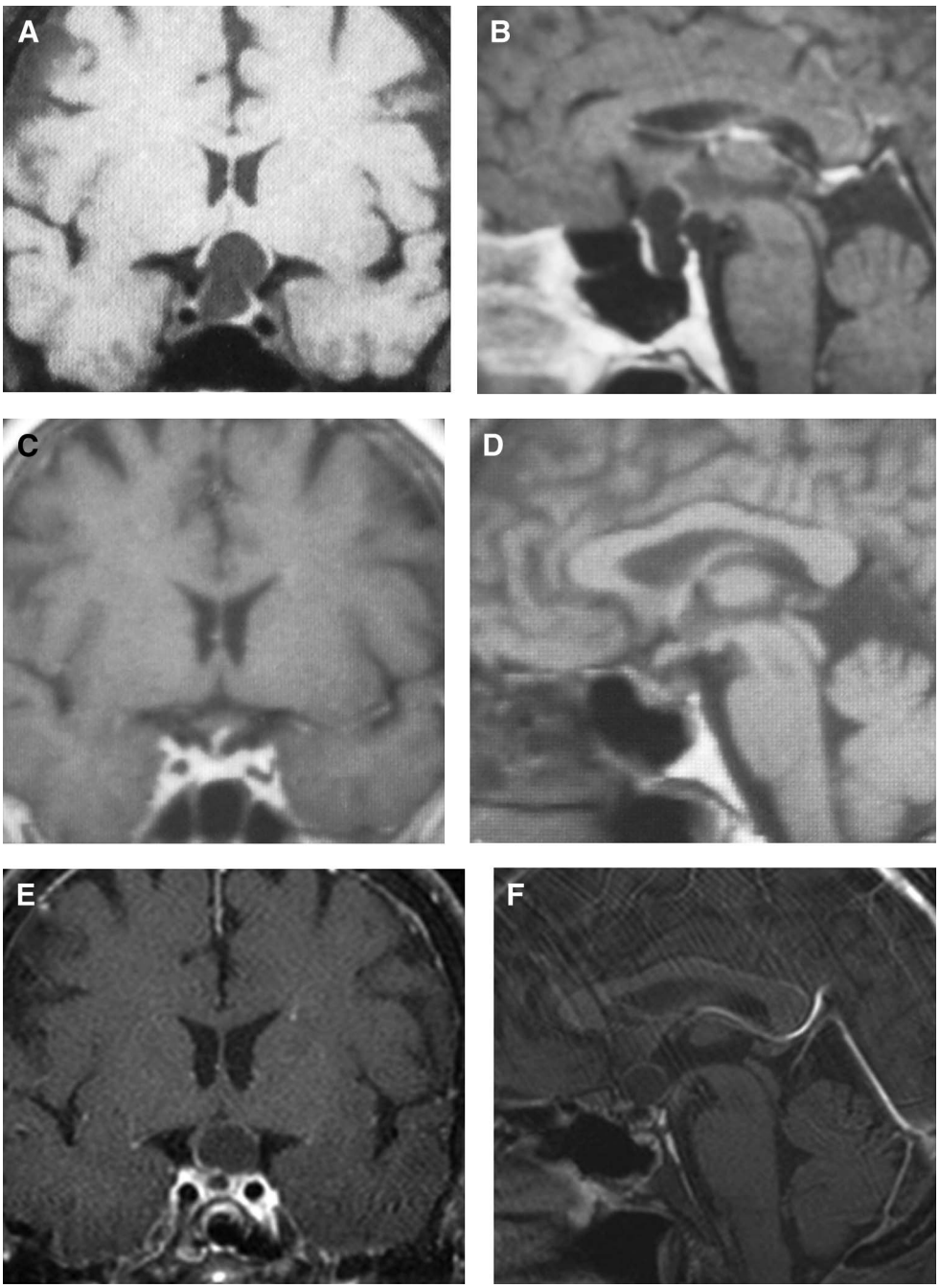

FIGURE 3. *Preoperative and postoperative imaging of a sellar Rathke cleft cyst with suprasellar extension (type II).* **A** *and* **B**, *preoperative T1-weighted gadolinium–enhanced coronal and sagittal MRIs demonstrating a 1.7-cm low-protein type II cyst in a 74-year-old woman.* **C** *and* **D**, *postoperative T1-weighted gadolinium-enhanced coronal and sagittal MRIs demonstrating resection of the cyst.* **E** *and* **F**, *after 70 months, the cyst had recurred to the same size as before surgery along with the patient's bitemporal hemianopsia, but the patient declined surgery at this time.*

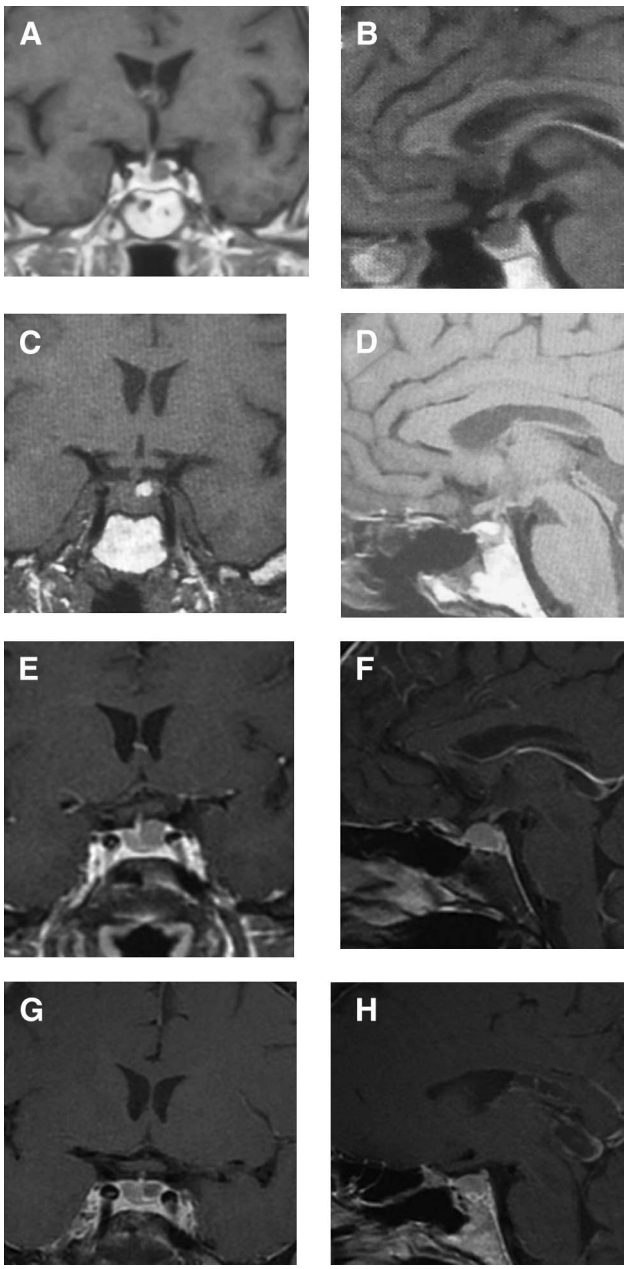

FIGURE 4. *Preoperative and postoperative imaging of a purely suprasellar Rathke cleft cyst (type III).* **A** *and* **B**, *preoperative T1-weighted gadolinium-enhanced coronal and sagittal MRIs demonstrating a 7-mm low-protein type III cyst in a 64-year-old man.* **C** *and* **D**, *postoperative T1-weighted gadolinium-enhanced coronal and sagittal MRIs demonstrating drainage of the cyst, as evidenced by a change in signal characteristics.* **E** *and* **F**, *after 30 months, the cyst had recurred to the same size as before surgery, along with the patient's visual symptoms.* **G** *and* **H**, *the cyst was redrained, and the patient's visual symptoms again improved.*

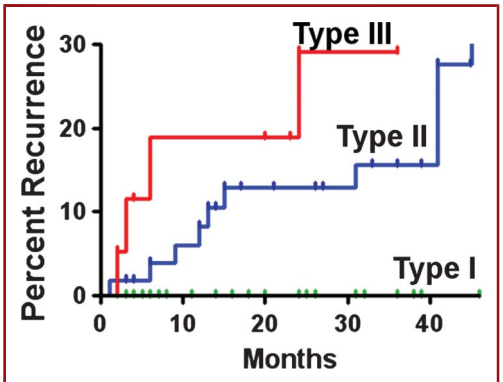

FIGURE 5. *Recurrence rates of different types of Rathke cleft cysts. Kaplan-Meier analysis of rates of radiographic recurrence vs time in months of Rathke cleft cysts that were sellar (type I; green), sellar with suprasellar extension (type II; blue), and suprasellar (type III; red). There was a significant difference (*$P < .001$*) between the recurrence of type I and II cysts and between the recurrence of type I and III cysts (*$P < .001$*), whereas the difference between the recurrence of type II and III cysts was not statistically significant (*$P = .5$*).*

the diaphragma sella in the suprasellar cistern. It is therefore thought that purely suprasellar RCCs arise from a remnant of the Rathke pouch within the pars tuberalis in the suprasellar cistern (Figure 1).[26,30,43] In this series of consecutive surgically managed RCCs over a 20-year period at our institution, we report the largest collection of purely suprasellar RCCs to date (Table 3). We divided RCCs into 3 distinct anatomical subgroups to distinguish purely suprasellar RCCs from sellar-based RCCs with and without suprasellar extension (Figure 2). We show that this classification system can be used both to characterize preoperative symptoms and to prognosticate surgical outcomes.

Before this series, the largest series of surgically treated RCCs was reported by Aho et al[6] in 2005, Lillehei et al[44] in 2010, and Benveniste et al[7] in 2004. Aho et al[6] studied 118 RCCs and reported a 49% incidence of preoperative visual dysfunction and 53% incidence of endocrinopathy. Complete cyst decompression was achieved in 97% of patients in this series, resulting in improved vision in 97% of patients with preoperative visual impairments. Aho et al did not specify cyst location in their report. Lillehei et al[44] reported a series of 82 surgically managed RCCs with presenting symptoms of headache in 68%, visual dysfunction in 35%, and endocrinopathy in 56%. They reported improved headaches in 71% and improved vision in 83%, as well as improvement in various endocrinopathies in 33% to 94% of patients. They did not characterize the anatomic location of their RCCs. Benveniste et al[7] reported a series of 62 surgically managed RCCs. Among these patients, 71% presented with headache, 55% presented with endocrinopathies, and 16% presented with visual complaints. Complete cyst decompression was achieved in 53% of patients in the Benveniste et al series, resulting in 91%

TABLE 2. Predictors of Rathke Cleft Cyst Recurrence

Variable[a]	Univariate Analysis		Multivariate Analysis	
	Hazard Ratio (95% Confidence Interval)	P[b]	Hazard Ratio (95% Confidence Interval)	P[b]
Primary variables				
Cyst type	NA	**<.001**		
Type III vs II	1.2 (0.9-1.3)	.5	1.2 (0.6-1.5)	.6
Type III/II combined vs I	2.5 (1.6-3.9)	**<.001**	2.6 (1.8-4.1)	**.004**
Cyst size (per 1-cm diameter)	2.4 (1.1-5.4)	.06	2.7 (0.6-11.8)	.2
Secondary variables				
Squamous metaplasia	1.8 (0.5-7.8)	.5		
Age (per decade)	1.3 (1.0-1.6)	.2		
Sex (male)	1.7 (0.8-2.0)	.6		
Inflammation	1.8 (0.6-5.8)	.5		
Use of fat graft	1.0 (0.5-2.5)	.9		
Ethanol irrigation	0.7 (0.4-1.7)	.5		

[a]Primary variables were those that pretest hypotheses suggested would contribute to recurrence risk, whereas secondary variables were not suspected to contribute to recurrence risk.
[b]Significant *P* values ($P < .03$ for univariate analysis, $P < .05$ for multivariate analysis) are indicated in bold.

improvement in headaches and 70% improvement in visual symptoms. Twenty-seven percent of the RCCs were confined to the sella, (type I RCCs); 73% were both sellar and suprasellar (type II); and none were purely suprasellar (type III). Surgical outcomes based on cyst location were not reported.

In our series, we found a trend toward greater preoperative visual dysfunction in purely suprasellar (type III) RCCs, a finding that is consistent with the anatomical location of these lesions above the diaphragma sella in close proximity to the optic nerve. Interestingly, 2 of the 76 type I RCCs presented with visual disturbance. This would not be predicted on the basis of the purely sellar location of these RCCs, but review of these patients' preoperative MRIs showed displacement of the pituitary gland superiorly into the optic chiasm. These patients' visual dysfunction also improved with cyst decompression, further confirming that their visual dysfunction was related to their RCC. There were no significant differences in the incidence of hypopituitarism among these subgroups, perhaps because none of the 3 types of RCCs truly arise in the anterior lobe of the pituitary gland and all must therefore exert mass effect adjacent to rather than from within the anterior lobe of the gland the way an adenoma does. In other words, suprasellar RCCs may be as capable of exerting mass effect on the underlying anterior lobe of the pituitary gland as sellar RCCs growing in the pars intermedia behind the anterior lobe. Surgically, we found that purely suprasellar RCCs were more difficult to drain completely than sellar-based RCCs. This coincided with significantly poorer outcomes with respect to resolution of headaches and visual dysfunction. Interestingly, rates of improvement of laboratory hypopituitarism did not vary with cyst location, again suggesting that all RCCs cause mass effect on the anterior lobe by growing adjacent to rather than from within the anterior lobe. Thus, despite a lesser volumetric reduction, decompressing type III RCCs from above the pituitary is as effective at normalizing endocrine function as decompressing type I RCCs from behind the pituitary.

Regardless of the surgical approach chosen, treatment of suprasellar lesions is more difficult because of the close proximity to vital structures like the optic chiasm and pituitary stalk. When using an endonasal approach, as in this report, the surgeon must typically traverse the tuberculum sella and sometimes the planum sphenoidale[16] to reach the cyst in the suprasellar cistern. Unlike an excision of the contents of sellar-based RCCs, where the optic nerve sits above the surgical corridor and is not seen during the operation, the optic nerve typically lies in closer proximity to suprasellar RCCs and must be carefully protected during cyst decompression. There were no incidences of optic nerve injury from decompression of type III RCCs, suggesting that the poorer rates of postoperative visual dysfunction improvement were due to lower likelihood of complete decompression. Several reports of purely suprasellar RCCs have described pterional or frontal craniotomies to obtain access to the suprasellar region for cyst decompression.[33] A craniotomy is more invasive than an endonasal approach and involves retraction of the frontal and temporal lobes. Furthermore, it is not yet clear if a craniotomy provides higher success rates for suprasellar RCCs than an endonasal approach. Endonasal endoscopic techniques for suprasellar lesions like meningiomas have been well described recently[34,36,37,45] and were applied to 3 of the cases in this series. This technique may allow higher rates of complete removal of cyst contents while providing a minimally invasive approach, as demonstrated by Madhok et al[16] in a series of 33 RCCs (20 sellar, 10 sellar with suprasellar extension, and 3 purely suprasellar) that were drained through an endoscopic endonasal approach, with

TABLE 3. Summary of Prior Reports of Purely Suprasellar Rathke's Cleft Cysts[a]

Study	Age, y/Sex	Presentation	Laboratory Hypopituitarism	Cyst Size, cm	Operation	Cyst Contents	Cyst Epithelium	Outcome	Recurrence[b]
Frazier and Alpers,[17] 1934	52/M	HA, VD	NR	NR	Crani	Brownish	Ciliated columnar	Improved HA and vision	NR
Eisenberg et al,[21] 1976	10/M	Impaired growth, frequent urination	Hypothyroid, hypocortisolemia	2	Crani	Opalescent, mucinous	Ciliated columnar	Postoperative DI	NR
Palma and Celli,[22] 1983	17/F	VD	Decreased LH/FSH	NR	Crani	Clear	Cuboidal	Some visual improvement, persistent low LH/FSH	NR
Rout et al,[23] 1983	19/F	HA, VD, amenorrhea, polyuria, polydipsia	NR	NR	Crani	Yellowish pultaceous	Ciliated columnar	Improved vision, persistent amenorrhea	No
Barrow et al,[26] 1985	35/F	HA, VD	Hyperprolactinemia	NR	Crani	Thick, yellow-tinged, white fluid	Ciliated columnar; plus squamous metaplasia	Vision returned to normal; decreased prolactin	No
	31/M	VD, impotence	Hypothyroid, hypocortisolemia, hypotestosteronism	NR	Crani	Thick, yellow-tinged, white fluid	Squamous metaplasia	Vision returned; still on thyroid and testosterone replacement	No
	13/M	VD	Panhypopituitarism with DI	NR	TS	Thick, yellowish	Columnar	Improved visual acuity but persistent VD and panhypopituitarism	No
Pangopoulos et al,[28] 1989	29/F	Panic episodes, depression	NR	NR	Crani	Mucinous	Cuboidal	No further panic episodes, persistent depression	No
	30/F	Infertility, galactorrhea	Hyperprolactinemia	NR	TS	Mucinous	NR	Normalized prolactin	No
Itoh and Usui,[30] 1992	21/F	HA/VD/fatigue/ menstrual irregularity	NR	NR	Crani	Clear, mucinous	Ciliated cuboidal	Improved symptoms	No
Cavallo et al,[31] 1993	26/F	HA, polydipsia, nocturia, oligomenorrhea	NR	2.9	NR	Milky	Ciliated cuboidal and pseudostratified columnar	Improved symptoms	NR
Graziani et al,[32] 1995	39/F	Amnestic episode	NR	1	Crani	Clear	Columnar	NR	NR
	40/F	HA	NR	2	Crani	Clear	Columnar	NR	NR
Mukherjee et al,[11] 1997	37/F	VD, amenorrhea	Hyperprolactinemia	NR	TS	Yellow, mucinous	Ciliated cuboidal	NR	No
Rincon et al,[33] 1999	29/F	VD, HA	NR	1.2	Crani	White, mucinous	Columnar	Transient DI, resolution of symptoms	NR
Kim et al,[34] 2000	41/F	VD, HA	Normal	NR	TS	NR	Ciliated columnar	NR	NR
Wenger et al,[43] 2001	58/M	Vertigo, decreased libido	Normal	1.2	Crani	White mucinous	Cuboidal	Resolution of symptoms	NR
Nakahara et al,[35] 2004	66/F	HA	Normal	NR	ETV	Cloudy mucinous	NR	NR	No
	73/M	VD	Hypopituitarism	NR	ETV	NR	NR	NR	No
Laufer et al,[38] 2007	53/F	VD	NR	1.1	ETS	NR	NR	Transient postoperative DI, hypocortisolemia, and blurry vision, all of which resolved	No

[a]Crani, craniotomy; DI, diabetes insipidus; ETS, endoscopic transsphenoidal; ETV, endoscopic transventricular; FSH, follicle-stimulating hormone; HA, headache; LH, lutenizing hormone; NR, not recorded; TS, transsphenoidal; VD, visual deficit. Other cases of purely suprasellar Rathke cleft cysts have been reported as part of a larger series that did not comment on individual patient characteristics.[10,13,16,36,37,39,40]

[b]Recurrence within the follow-up period of each individual study.

only 2 recurrences reported. However, the authors did not attempt to correlate recurrences and rate of symptomatic improvement with cyst location.

We report Kaplan-Meier 3-year recurrence rates of 0%, 16%, and 29% for type I, II, and III RCCs, respectively, with recurrence occurring in 11% of the total population. Although our overall recurrence rate is similar to that in many prior reports,[6,7,14,40,44,46-48] it should be noted that the range of reported recurrence rates in the literature is quite large,[11,12,16,49-51] with 1 study reporting none[52] and another reporting 42%.[15] The majority of our patients received their first postoperative MRI at 6 weeks, raising the possibility that some early recurrences before 6 weeks could be designated residual cysts rather than recurrent cysts. However, prior studies have shown that cyst reaccumulation typically does not occur before this 6-week interval,[6,7,41] and none of our 15 patients who underwent immediate postoperative imaging exhibited a recurrence at their first subsequent MRI. Of note, prior reports have suggested that the use of an abdominal fat graft for closure has actually been associated with higher rates of recurrence.[6] It is theorized that an abdominal fat or fascial graft may prevent marsupialization of a cyst and lead to reaccumulation. We found that use of an abdominal fat graft, which occurred in 62 cases in our series, was not associated with recurrence in a multivariate analysis.

Pathologically, RCCs are characterized by a columnar or cuboidal epithelium,[53] and findings of cyst wall inflammation or squamous metaplasia have been reported.[7,54] In this series, we also found that purely suprasellar RCCs were distinct from sellar-based RCCs with regard to histology. Type III RCCs were more likely to have evidence of squamous metaplasia compared with sellar-based RCCs, although this finding was not associated with increased recurrence rate in our multivariate analysis. Other authors have reported on the significance of such histological findings. Benveniste et al[7] showed that both cyst wall inflammation and squamous cell metaplasia were associated with increased recurrence rate. Hama et al[54] specifically examined changes in the epithelium of RCCs and found that the presence of inflammation led to stratified cyst epithelium and was associated with hypophysitis and hypopituitarism. Two potential causes of RCC epithelial inflammation have been identified: bacterial infection and aseptic irritation. We recently reported a series of infected RCCs and showed that the surgeon's suspicion of bacterial infection was a strong predictor of cyst recurrence.[41] Conversely, there have been several reports of aseptic inflammation thought to be associated with irritation from the mucinous contents of a cyst.[54] Interestingly, although we found a higher rate of squamous metaplasia in type III RCCs, we also found that this subgroup was less likely to have proteinaceous fluid on the basis of preoperative MRI. It is possible that the higher squamous metaplasia in type III RCCs may reflect the observation by Harrison et al[55] that RCCs and craniopharyngiomas are part of a continuum of epithelium-lined cystic lesions and the subsequent finding by Aho et al[6] that RCCs with squamous metaplasia have a natural history in terms of recurrence rates that resembles that of craniopharyngiomas. Although we did not find squamous metaplasia to be predictive of a higher recurrence rate in this series, given their suprasellar location, it is possible that the squamous metaplasia we found in type III RCCs may reflect the fact that type III RCCs are closer to the craniopharyngioma side of the spectrum of cystic epithelium-lined sellar and suprasellar lesions. On the other hand, the tendency of type III RCCs to have less proteinaceous fluid may reflect reduced levels of infection in these cysts compared with type I RCCs. Although we excluded RCCs in which the surgeon suspected infection from this analysis, a review of our previously reported RCC cases in which the surgeon suspected infection[41] revealed that 10% of infected RCCs were type III (data not shown), similar to the frequency reported in this article. Regardless, it is possible that our series contains some infected RCCs that did not evoke suspicion for infection. Further work is needed to clarify these findings.

CONCLUSION

Although large symptomatic suprasellar RCCs such as those described here clearly warrant treatment, there are unique challenges in their neurosurgical treatment owing to their intimate proximity to the optic chiasm and pituitary stalk. In particular, our retrospective review found that, compared with sellar RCCs, RCCs with a suprasellar component are more difficult to remove completely and to obtain symptomatic resolution. The RCCs with a suprasellar component also carry a higher recurrence rate. These findings suggest that RCCs with a suprasellar component are best handled by experienced pituitary surgeons and that the expectations of cure and symptomatic resolution should be carefully discussed with patients.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Prabhu VC, Brown HG. The pathogenesis of craniopharyngiomas. *Childs Nerv Syst*. 2005;21(8-9):622-627.
2. Shanklin WM. On the presence of cysts in the human pituitary. *Anat Rec*. 1949;104(4):379-407.
3. Fager CA, Carter H. Intrasellar epithelial cysts. *J Neurosurg*. 1966;24(1):77-81.
4. McGrath P. Cysts of sellar and pharyngeal hypophyses. *Pathology*. 1971;3(2):123-131.
5. Teramoto A, Hirakawa K, Sanno N, Osamura Y. Incidental pituitary lesions in 1,000 unselected autopsy specimens. *Radiology*. 1994;193(1):161-164.
6. Aho CJ, Liu C, Zelman V, Couldwell WT, Weiss MH. Surgical outcomes in 118 patients with Rathke cleft cysts. *J Neurosurg*. 2005;102(2):189-193.
7. Benveniste RJ, King WA, Walsh J, Lee JS, Naidich TP, Post KD. Surgery for Rathke cleft cysts: technical considerations and outcomes. *J Neurosurg*. 2004;101(4):577-584.
8. Zada G, Lin N, Ojerholm E, Ramkissoon S, Laws ER. Craniopharyngioma and other cystic epithelial lesions of the sellar region: a review of clinical, imaging, and histopathological relationships. *Neurosurg Focus*. 2010;28(4):E4.
9. Voelker JL, Campbell RL, Muller J. Clinical, radiographic, and pathological features of symptomatic Rathke's cleft cysts. *J Neurosurg*. 1991;74(4):535-544.

10. Ross DA, Norman D, Wilson CB. Radiologic characteristics and results of surgical management of Rathke's cysts in 43 patients. *Neurosurgery*. 1992;30(2):173-178.
11. Mukherjee JJ, Islam N, Kaltsas G, et al. Clinical, radiological and pathological features of patients with Rathke's cleft cysts: tumors that may recur. *J Clin Endocrinol Metab*. 1997;82(7):2357-2362.
12. Frank G, Sciarretta V, Mazzatenta D, Farneti G, Modugno GC, Pasquini E. Transsphenoidal endoscopic approach in the treatment of Rathke's cleft cyst. *Neurosurgery*. 2005;56(1):124-128.
13. Sade B, Albrecht S, Assimakopoulos P, Vezina JL, Mohr G. Management of Rathke's cleft cysts. *Surg Neurol*. 2005;63(5):459-466.
14. Koutourousiou M, Grotenhuis A, Kontogeorgos G, Seretis A. Treatment of Rathke's cleft cysts: experience at a single centre. *J Clin Neurosci*. 2009;16(7):900-903.
15. Raper DM, Besser M. Clinical features, management and recurrence of symptomatic Rathke's cleft cyst. *J Clin Neurosci*. 2009;16(3):385-389.
16. Madhok R, Prevedello DM, Gardner P, Carrau RL, Snyderman CH, Kassam AB. Endoscopic endonasal resection of Rathke cleft cysts: clinical outcomes and surgical nuances. *J Neurosurg*. 2010;112(6):1333-1339.
17. Frazier CH, Alpers BJ. Tumors of Rathke's cleft (hitherto called tumors of Rathke's pouch). *Arch Neurol and Psychiatry*. 1934;32(5):973-984.
18. Bayoumi ML. Rathke's cleft and its cysts. *Edinb Med J*. 1948;55(12):745-749.
19. Naiken VS, Tellem M, Meranze DR. Pituitary cyst of Rathke's cleft origin with hypopituitarism. *J Neurosurg*. 1961;18(5):703-708.
20. Fairburn B, Larkin IM. A cyst of Rathke's cleft. *J Neurosurg*. 1964;21:223-225.
21. Eisenberg HM, Sarwar M, Schochet S Jr. Symptomatic Rathke's cleft cyst: case report. *J Neurosurg*. 1976;45(5):585-588.
22. Palma L, Celli P. Suprasellar epithelial cyst. Case report. *J Neurosurg*. 1983;58(5):763-765.
23. Rout D, Das L, Rao VR, Radhakrishnan VV. Symptomatic Rathke's cleft cysts. *Surg Neurol*. 1983;19(1):42-45.
24. Hiramatsu K, Ohnishi H, Nikaido Y, Fujita T, Kawaguchi S. Suprasellar epithelial cyst associated with cerebral aneurysm: case report [in Japanese]. *Neurol Med Chir (Tokyo)*. 1984;24(5):359-363.
25. Yamamoto M, Takara E, Imanaga H, Jimbo M, Kubo O. Rathke's cleft cyst: report of two cases [in Japanese]. *No Shinkei Geka*. 1984;12(5):609-616.
26. Barrow DL, Spector RH, Takei Y, Tindall GT. Symptomatic Rathke's cleft cysts located entirely in the suprasellar region: review of diagnosis, management, and pathogenesis. *Neurosurgery*. 1985;16(6):766-772.
27. Ishii T, Yamasaki T, Tanaka J, Tanaka S, Hori T, Muraoka K. Rathke's cleft cyst: report of three cases [in Japanese]. *No Shinkei Geka*. 1987;15(4):451-456.
28. Panagopoulos KP, Jolesz FA, el-Azouzi M, Black PM. Mucinous cysts of the pituitary stalk: report of two cases. *J Neurosurg*. 1989;71(2):276-278.
29. Yuge T, Shigemori M, Tokutomi T, et al. Entirely suprasellar symptomatic Rathke's cleft cyst [in Japanese]. *No Shinkei Geka*. 1991;19(3):273-278.
30. Itoh J, Usui K. An entirely suprasellar symptomatic Rathke's cleft cyst: case report. *Neurosurgery*. 1992;30(4):581-584.
31. Cavallo AV, Murphy MA, McKelvie PA, Cummins JT. An epithelial cyst of the suprasellar region. *Aust N Z J Surg*. 1993;63(6):490-493.
32. Graziani N, Dufour H, Figarella-Branger D, Donnet A, Bouillot P, Grisoli F. Do the suprasellar neurenteric cyst, the Rathke cleft cyst and the colloid cyst constitute a same entity? *Acta Neurochir (Wien)*. 1995;133(3-4):174-180.
33. Rincon JL, Nunes J, Camuto P, Goodrich I. Intracranial approach to suprasellar Rathke's cleft cyst. *Skull Base Surg*. 1999;9(1):71-73.
34. Kim J, Choe I, Bak K, Kim C, Kim N, Jang Y. Transsphenoidal supradiaphragmatic intradural approach: technical note. *Minim Invasive Neurosurg*. 2000;43(1):33-37.
35. Nakahara Y, Koga H, Maeda K, Takagi M, Tabuchi K. Neuroendoscopic transventricular surgery for suprasellar cystic mass lesions such as cystic craniopharyngioma and Rathke cleft cyst. *Neurol Med Chir (Tokyo)*. 2004;44(8):408-413.
36. Dusick JR, Esposito F, Kelly DF, et al. The extended direct endonasal transsphenoidal approach for nonadenomatous suprasellar tumors. *J Neurosurg*. 2005;102(5):832-841.
37. de Divitiis E, Cavallo LM, Cappabianca P, Esposito F. Extended endoscopic endonasal transsphenoidal approach for the removal of suprasellar tumors, part 2. *Neurosurgery*. 2007;60(1):46-58.
38. Laufer I, Anand VK, Schwartz TH. Endoscopic, endonasal extended transsphenoidal, transplanum transtuberculum approach for resection of suprasellar lesions. *J Neurosurg*. 2007;106(3):400-406.
39. Wen L, Hu LB, Feng XY, et al. Rathke's cleft cyst: clinicopathological and MRI findings in 22 patients. *Clin Radiol*. 2010;65(1):47-55.
40. Nishioka H, Haraoka J, Izawa H, Ikeda Y. Headaches associated with Rathke's cleft cyst. *Headache*. 2006;46(10):1580-1586.
41. Tate MC, Jahangiri A, Blevins L, Kunwar S, Aghi MK. Infected Rathke cleft cysts: distinguishing factors and factors predicting recurrence. *Neurosurgery*. 2010;67(3):762-769
42. Kleinschmidt-DeMasters BK, Lillehei KO, Stears JC. The pathologic, surgical, and MR spectrum of Rathke cleft cysts. *Surg Neurol*. 1995;44(1):19-26.
43. Wenger M, Simko M, Markwalder R, Taub E. An entirely suprasellar Rathke's cleft cyst: case report and review of the literature. *J Clin Neurosci*. 2001;8(6):564-567.
44. Lillehei KO, Widdel L, Arias Astete CA, Wierman ME, Kleinschmidt-Demasters BK, Kerr JM. Transsphenoidal resection of 82 Rathke cleft cysts: limited value of alcohol cauterization in reducing recurrence rates. *J Neurosurg*. 2010;114(2):310-317.
45. Dehdashti AR, Ganna A, Witterick I, Gentili F. Expanded endoscopic endonasal approach for anterior cranial base and suprasellar lesions: indications and limitations. *Neurosurgery*. 2009;64(4):677-687.
46. Billeci D, Marton E, Tripodi M, Orvieto E, Longatti P. Symptomatic Rathke's cleft cysts: a radiological, surgical and pathological review. *Pituitary*. 2004;7(3):131-137.
47. Shin JL, Asa SL, Woodhouse LJ, Smyth HS, Ezzat S. Cystic lesions of the pituitary: clinicopathological features distinguishing craniopharyngioma, Rathke's cleft cyst, and arachnoid cyst. *J Clin Endocrinol Metab*. 1999;84(11):3972-3982.
48. Kim JE, Kim JH, Kim OL, et al. Surgical treatment of symptomatic Rathke cleft cysts: clinical features and results with special attention to recurrence. *J Neurosurg*. 2004;100(1):33-40.
49. Eguchi K, Uozumi T, Arita K, et al. Pituitary function in patients with Rathke's cleft cyst: significance of surgical management. *Endocr J*. 1994;41(5):535-540.
50. Cohan P, Foulad A, Esposito F, Martin NA, Kelly DF. Symptomatic Rathke's cleft cysts: a report of 24 cases. *J Endocrinol Invest*. 2004;27(10):943-948.
51. Dusick JR, Fatemi N, Mattozo C, et al. Pituitary function after endonasal surgery for nonadenomatous parasellar tumors: Rathke's cleft cysts, craniopharyngiomas, and meningiomas. *Surg Neurol*. 2008;70(5):482-490.
52. el-Mahdy W, Powell M. Transsphenoidal management of 28 symptomatic Rathke's cleft cysts, with special reference to visual and hormonal recovery. *Neurosurgery*. 1998;42(1):7-16.
53. McLendon RE, Bigner DD, Bigner SH, Provenzale JM. *Pathology of Tumors of the Nervous System: A Guide to Histologic Diagnosis*. London, UK: Arnold; 2000.
54. Hama S, Arita K, Nishisaka T, et al. Changes in the epithelium of Rathke cleft cyst associated with inflammation. *J Neurosurg*. 2002;96(2):209-216.
55. Harrison MJ, Morgello S, Post KD. Epithelial cystic lesions of the sellar and parasellar region: a continuum of ectodermal derivatives? *J Neurosurg*. 1994;80(6):1018-1025.

COMMENTS

This large, well-documented series adds worthwhile information to the literature. I am particularly pleased to see the breakdown of these Rathke cleft cysts (RCCs) into the 3 types. As the authors demonstrate, there are significant differences in presentation and results among the different types. This information is important when discussing potential results with patients and when we review our own series. Primarily suprasellar RCCs, I believe, fit into a continuum of ectodermal derivatives, including squamous metaplasia and craniopharyngioma, as we published in 1994.[1] They may require more aggressive resections than we have previously advised for predominately sellar-based RCCs when aggressive resection leads to higher incidence of postoperative hypopituitarism.

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This large series of colloid cysts of the third ventricle adds useful information about the management of these relatively rare entities and tailoring treatment to their anatomical position. It is worth noting that, for whatever reason, there has always seemed to be a rather higher recurrence rate in North American series than in European series. Although I have no direct experience with the use of absolute alcohol in this setting, I have seen serious problems related to its use in trigeminal nerve ablation in the distant past and thus add serious cautions about its use.

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