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High prevalence of adrenal insufficiency at diagnosis and headache recovery in surgically resected Rathke's cleft cysts—a large retrospective single center study

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Abstract

Background Rathke's cleft cysts (RCC) are lesions that arise from Rathke's pouch. Though frequently incidental, resulting symptoms in a minority of cases are indicators for surgical resection, which may prove beneficial.

Objective To characterize a cohort of surgically-resected RCC cases at Oregon Health & Science University; tabulate associated hormonal imbalances and symptoms, possible symptom reversal with surgery, determine recurrence risk; identify predictors of recurrence and headache improvement.

Method Electronic records of all RCC resected cases (from 2006–2016; 11 years) were retrospectively reviewed. Patients had been evaluated by one neuroendocrinologist using a uniform protocol.

Results A pathological RCC diagnosis was established in 73 of 814 (9%) surgical pituitary cases. The RCC cohort was 77% ($n = 56/73$) female, mean age was 39.5 ± 14.9 years at first surgery, and at presentation headache was reported in 88% and visual defects/diplopia in 18% of patients. Initial RCC maximum diameter was 1.3 ± 0.7 cm. The most frequent hormonal deficit was cortisol; 24% of patients had a new adrenal insufficiency (AI) diagnosis, however, 36% also had AI at 3 months post-operatively. Mean follow up was 4.0 ± 4.5 years. Two-thirds of patients (41/62) had headache improvement 3 months post-operatively. Post-operative imaging revealed no residual cyst in 58% (38/65). In those patients with no residual RCC, 29% had recurrence and 71% had long lasting cure. From the 42% (27/65) of patients with residual cyst on post-operative imaging; 59% (16/27) remained stable, 26% (7/27) progressed and 15% (4/27) regressed.

Conclusion Symptomatic RCC present mostly in women, with a high proportion reporting headaches. Prevalence of AI at diagnosis is high. Surgery may not achieve adrenal axis recovery, but renders a high percentage of headache improvement. Approximately 25% of RCC will recur by 4 years postoperatively. Clinicians should cautiously screen patients with symptomatic RCC, regardless of lesion size for AI.

Keywords Rathke's cleft cysts · Pituitary cyst · Pituitary lesions · Adrenal insufficiency · Transsphenoidal surgery · Headache

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Introduction

Rathke's cleft cysts (RCC) are benign pituitary cystic lesions arising from the embryologic remnants of Rathke's pouch. RCC are commonly (80%) located within the pars intermedia, an area between the anterior and posterior pituitary gland [1, 2]. This area seems negligible in size and function in humans, yet interestingly persists in mammals where it consists of corticotroph cells and plays a role in neurogenic stress response [3].

The majority of RCCs are small and asymptomatic; usually found incidentally on brain imaging studies (magnetic resonance imaging; MRI and computed tomography; CT) [4, 5]. With ongoing improvements in imaging, pituitary incidentalomas are now found in 1 of 10 of brain imaging studies [6] with RCC as the second most common pituitary abnormality noted after pituitary adenomas.[7] At autopsy RCC are found in up to 20% of incidental pituitary lesions [8].

A minority of RCC are symptomatic, mostly caused by cyst enlargement and local compression of adjacent structures, manifested by headaches, vision disturbances secondary to optic chiasm compression, and pituitary dysfunction [5]. In these cases, surgical resection via transsphenoidal approach (TSS) may be indicated, in order to determine a precise diagnosis and improve or resolve patients' symptoms. The surgical aim is cyst evacuation, with or without cyst wall removal, or biopsy [2].

The main objective of this study was to characterize a cohort of surgically resected RCC at a single institution. Presenting symptoms, hormonal deficiencies at baseline and recovery rate after pituitary surgery are reviewed. Additionally, we aimed to identify predictors of adrenal insufficiency (AI) at baseline, to characterize subpopulations of patients who improve post-surgery, to assess progression after surgery, and also to determine the recurrence risk of TSS-resected RCC.

Methods

Subjects

Electronic medical records (EMR) of all patients who underwent surgical resection for symptomatic RCC between 2006 and 2016 at Oregon Health & Science University (OHSU), were retrospectively reviewed. This time period was selected since both implementation of EMR and a unified neuroendocrinology protocol for evaluation of all pituitary lesions was implemented in 2006. The study was approved by the OHSU Institutional Review Board with a waiver of subject consent.

A definitive or probable diagnosis of RCC was made by histological examination of individual RCC samples, which was undertaken by one of the three dedicated neuropathologists. Definitive diagnosis was made if cyst wall lined with columnar ciliated epithelium was observed [9]. Probable diagnosis was based on absence of lining epithelium with material consistent with cyst content, and absence of adenomatous pituitary tissue. Other types of pituitary cysts, as determined by neuropathologist (e.g., dermoid, epidermoid, arachnoid cysts) were excluded from the study analysis.

All patients had been evaluated by one of 3 OHSU neurosurgeons, the majority of surgeries were performed by neurosurgeon and author [J.C.] during the 11-year inclusion period. In most patients, surgical indications were: intractable headache, visual symptoms or progressive cyst volume. Surgical decision-making was individualized and consisted of cyst removal. Fenestration was not performed at the first surgery.

Clinical and hormonal evaluation was performed by a single neuroendocrinologist using a uniform protocol. Medical records were retrospectively reviewed by the first authors. Patients had pre-operative baseline insulin growth factor-1 (IGF-1) levels, hormonal evaluations of their adrenal, thyroid and gonadal axes, and prolactin (PRL) levels. Central AI diagnosis was based on abnormal cortisol response to 1 µg adrenocorticotropic hormone (ACTH) stimulation test (30 mins. stimulated cortisol < 16 µg/dL, or 16–18 µg/dL with compatible AI clinical signs and symptoms). Central hypothyroidism was defined as low free thyroxine and low or normal thyroid stimulating hormone. In men, central hypogonadism was defined as low testosterone and low or normal follicle stimulating hormone (FSH) and luteinizing hormone (LH). In premenopausal women central hypogonadism was defined as oligo- or amenorrhea, low estradiol, and low or normal FSH and LH. In postmenopausal women both an FSH and LH lower than the reference range for post-menopausal status, defined central hypogonadism. Multiple deficiencies was defined as having more than one hormonal deficiency as detailed above, also including IGF-1 lower than the age and sex adjusted reference. Growth hormone (GH) stimulation tests were not routinely performed in patients with multiple pituitary deficiency as low IGF1 is consistent with GH deficiency and GH stimulation test is considered optional in this context [10, 11]. Hyperprolactinemia was defined as elevated PRL above the normal range for sex. Central diabetes insipidus (DI) was diagnosed based on clinical presentation (polyuria, polydipsia) and inappropriate low urine osmolarity. All patients had undergone multiple brain MRI studies at; baseline, 3 and 12 months postoperatively, and at regular intervals thereafter. Based on anatomical location, RCC were categorized as intrasellar, suprasellar and intra/

suprasellar. Patients with brain MRI showing suprasellar cysts impinging on, or at risk of impingement of the optic chiasm based on the location and/or their large size, had a visual field testing performed by a neuroophthalmologist.

For outcome analysis, gross surgical cure was defined as no residual lesion on pituitary MRI. Recurrence was defined as new cystic growth after gross surgical cure or progression of residual RCC diameter of ≥2 mm, regression was defined as a decrease in size of ≥2 mm; in patients with post-operative follow-up > 3 months. If 3 month post-operative data was unavailable, 6 month post-operative data was used (5 patients). Four patients had their first surgery outside OHSU. For these 4 patients, the pathological diagnosis of RCC was based on histopathological analysis at OHSU; baseline hormonal evaluation was based on first hormonal evaluation at our institution, and outcome was based on local follow-up (which preceded the second surgery from 0 to 3 years). Hormonal and imaging data was included in analysis if previous clinical evaluation was available and complete, otherwise was considered missing.

Statistics

Results are expressed as mean ± standard deviation. Means were compared using an unpaired Student's t-test. For predictors of AI, headache recovery and recurrence, independent *T*-test, chi-square test, Linear regression analysis and Pearson correlation were also performed. Statistical analysis was undertaken using SPSS Statistics 24 (IBM Corp., Armonk, NY); *p* values were considered significant at <0.05.

Results

Study population

A total of 814 patients underwent TSS at OHSU in the 11–year time span under retrospective review. Of this total, 73 patients (9%, 73/814) had pathology documented RCC. There were 56 females/17 males (77% female), mean age at the first TSS was 39.5 ± 14.9 years (range 12–73 years, with 2 pediatric cases) (Table 1).

Clinical, biochemical, and radiological presentation

The main presenting clinical symptom was headache in 88% (63/72), while 18% (13/72) had visual field defects. Headache was more common in females than in males (91 vs 75% respectively). Twenty-two percent of patients reported a history of migraines, all presenting with headaches. Interestingly, chronic opioid use for pain, including headaches, was recorded in 34% (24/70) of patients.

Table 1 Characteristics of patients with surgically-resected Rathke's cleft cysts

Demographics	
Sex-female (%, *n*)	77 (56/73)
Age at first transphenoidal surgery (years ± SD)	39.5 ± 14.9
Follow-up (years ± SD)	4.0 ± 4.5
Presenting symptoms	
Headache (%, *n*)	88 (63/72)
Visual field defects (%, *n*)	18 (13/72)
Imaging characteristics	
Maximum cyst diameter, cm ± SD	1.3 ± 0.7
Localization—intra-sellar only (%, *n*)	65 (46/71)
Extra sellar component (%, *n*)	35 (25/71)
T1-hyperintense (%, *n*)	69 (27/39)
T2-hypointense (%, *n*)	45 (13/29)
T2-hyperintense (%, *n*)	38 (11/29)
Baseline biochemical evaluation	
Central AI—new diagnosis (%, *n*)	24 (16/68)
Central gonadotroph deficiency (%, *n*)	22 (14/65)
Hyperprolactinemia (%, *n*)	19 (12/63)
Central hypothyroidism (%, *n*)	4 (3/71)
Diabetes insipidus (%, *n*)	1.4 (1/71)
Multiple hormonal deficiencies (%, *n*)	14 (10/71)

Multiple endocrine dysfunctions were diagnosed on initial biochemical evaluation. Central AI was the most common (24%, 16/68), followed by central gonadotroph deficiency (22%, 14/65), hyperprolactinemia (19%, 12/63), central hypothyroidism (4%, 3/71), and rarely DI (1.4%, 1/71). Interestingly, isolated AI was observed more frequently than AI in the context of multiple hormonal deficiencies (56%, 9/16 vs 44%, 7/16; respectively). Central AI correlated with female gender ($r = .305$, $p = .02$), presence of other pituitary deficiencies (central hypogonadism, $r = .25$, $p = .04$; central hypothyroidism $r = .252$, $p = .034$) and opioid use ($r = .26$, $p = .036$).

Maximum RCC diameter on brain MRI was 1.3 ± 0.7 cm. The majority of the RCC were strictly intrasellar (65%, 46/71), while 35% (25/71) had an extrasellar component. RCC signal intensities were mostly hyperintense on T1-weighted images (69%, 27/39).

Patient outcome

There was a significant headache improvement after TSS in 66% of patients (41/62). However, no baseline characteristic was associated with postoperative headache recovery, including personal history of migraines, cyst size, demographics or gross surgical cure. Interestingly, cyst diameter at presentation did not correlate with headache improvement. Regardless of maximum cyst diameter (<1 cm,

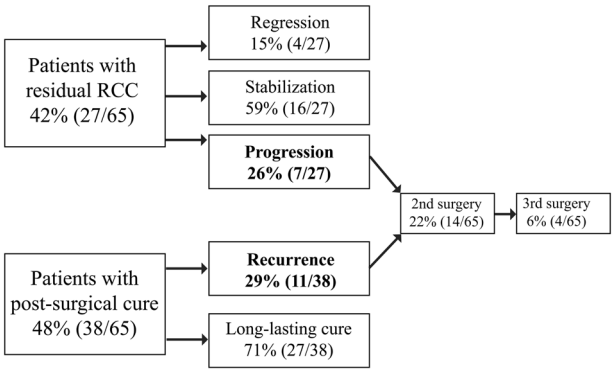

Fig. 1 Outcome of patients with surgically-resected Rathke's cleft cysts

Table 2 Predictors of recurrence of surgically-resected Rathke's cleft cysts ($n = 65$)

Variable	Non-recurrent cysts ($n = 47$)	Recurrent cysts ($n = 18$)	p value
Sex (% female)	70	83	0.29
Mean age (years ± SD)	38.6 ± 14.6	39.4 ± 16.3	0.87
Mean tumor size (cm ± SD)	1.30 ± 0.85	1.20 ± 0.53	0.67
Headaches (%)	89	72	0.049
T1 hyperintensity (%)	100	90	0.21
Extra-sellar component (%)	32	28	0.50
Baseline new AI (%)	19	22	0.19

1.0–1.5 cm, or >1.5 cm), all patients had a similar recovery rate, respectively 62, 60 and 83% (not significant); although patients with larger cysts did seem to benefit the most overall from surgical intervention.

Central AI at 3 months post-surgery was found in 36% of patients (24/66); 10 new cases (15%), 12 cases diagnosed prior to surgery (including 1 patient with AI post first surgery > 10 years prior). Two cases had no documented laboratory evaluation prior to surgery. From the 16 cases of central AI diagnosed during the initial work-up, 5 patients recovered at 3 months post-surgery (31%). Mean follow-up was 4.0 ± 4.5 years.

Post-operative imaging showed post-surgical cure (no residual RCC) in 58% of cases. From this group, 29% (11/38) developed recurrence, and 71% (27/38) had long lasting cure (Fig. 1). In the 42% of patients with persistent residual RCC (27/65) on long-term follow-up with sequential brain MRI; 16/27 (59%) remained stable, 7/27 (26%) progressed and 4/27 (15%) regressed. The rate of progression or recurrence was similar for those with patients with no residual RCC and those with persistent residual RCC, 26 vs. 29%, respectively.

Overall, 18 patients experienced cyst recurrence and progression; 22% (14/65) required a second, and 6% (4/65) a third surgery.

Recurrence was negatively correlated with baseline headaches ($r = 0.267$, $p = 0.024$). We observed less frequent headache in recurrent vs. non-recurrent cysts, but percentage was high in both groups (72 vs. 89% respectively). No correlation was observed with other demographics (female sex, age), presence of AI, or imaging characteristics (cyst size, T1 hyperintensity on brain MRI, presence of an extra-sellar component; Table 2).

Discussion

Clinical, biochemical, and radiological presentation

In this large retrospective single institution cohort with uniform hormonal evaluation, patients who underwent surgical intervention for symptomatic RCC were predominantly female, with a mean age at presentation of 40–50 years. These findings are similar to data published in previous studies [2, 4, 12, 13]. Moreover, given females have a higher prevalence of headaches, this sex profile in this cohort of symptomatic surgically-resected RCC, was not surprising.

In our cohort of patients, the most common initial symptom was headache (88%), and visual field defects were infrequent (18%). Headache had prompted brain imaging leading to a diagnosis of RCC in many patients. Headache has been previously reported as the common presenting complaint in patients with RCC requiring surgery affecting up to three quarters of study subjects [4, 13–18]. Conversely, Karavitaki et al., who examined a cohort of 33 patients, with a gender and age at diagnosis similar to this cohort, found that the most common presenting complaint was visual field defect (58%) [2]. Higher rate of visual fields defects could be attributed to a higher rate of suprasellar cysts [4], but referral bias may be a factor.

Not all RCC patients will require surgery. Here we present a selected RCC population who benefited from surgical intervention, based on intractable headaches, increasing RCC size or visual symptoms. This represents a small percentage of overall RCC, but a high proportion of symptomatic patients who will be encountered in clinical practice. In a recent large retrospective study, Sala and colleagues analyzed 2 cohorts; patients with RCC who underwent surgery (group A, 72 patients) vs. patients who did not require surgery for RCC (group B, 62 patients). In comparison to group B, group A had a higher rate of headaches at presentation, more visual impairment, endocrine dysfunction symptoms and pituitary hormonal abnormalities, larger cyst size at diagnosis with extrasellar extension ($p < 0.05$). In comparison to group A, group B had a higher rate of incidental diagnosis (48.4 vs. 12.5%, $p < 0.001$) [13].

Various pituitary deficiencies have been reported in previous studies, with small differences regarding the most common pituitary hormonal deficiencies, hyperprolactinemia, and DI [2, 13, 15–21]. Notably, in our study a GHD diagnosis had not been clearly established in all patients. In this study, AI was the most prevalent hormonal abnormality, diagnosed in 24% of patients. Kim et al., also showed that hypocortisolism was the most common pituitary dysfunction (40%) [4]. Sala et al., found that AI was the second most frequent hormonal deficit in patient who underwent surgery, and the most frequent in patients managed conservatively [13]. This finding is somewhat unexpected when compared with pituitary adenomas, since cysts size is overall relatively small and adrenal axis is usually more resistant to compressive effect. Opioid use could increase risk of AI in this population. Based on these findings, we emphasize the clinical necessity to test for adrenal reserve in a patient with a RCC, even a small RCC. However, AI in itself should not be an indication for surgery, since AI may or may not improve after intervention.

Our group has previously shown in a study looking at predictors of pituitary silent corticotroph adenomas (SCAs) that a subgroup of cystic SCAs may originate from the pars intermedia [22], similar to RCC. Some RCCs derived from the pars intermedia might contain a small number of corticotroph cells with low ACTH secretion ability, not sufficient for positive histology ACTH immunostaining. Even if few ACTH cells are present, cortisol axis can be disrupted and adenoma/cyst removal could subsequently lead to additional post-operative AI.

We hypothesize that headache and AI at presentation could be associated with higher pericystic inflammation in symptomatic RCC patients. There are a few case reports of acute central AI, and hypophysitis in the context of RCC [23–30]. The proposed theories are that inflammatory changes within the cyst (e.g., due to hemorrhage), compression of the pituitary gland, and cystic fluid leak cause pericystic inflammation and rarely aseptic meningitis [23–30]. Inflammation added to compressive effect in large cysts are likely responsible for the multiple pituitary hormonal abnormalities in the context of symptomatic RCC.

Rathke's cleft cysts are visualized on brain imaging studies (CT and MRI). On MRI, RCC are usually described as well circumscribed sellar and/or suprasellar lesions located in the pars intermedia of the pituitary gland. The signal intensity depends on the cyst content and can be hypo-/iso-/hyperintense. Homogeneous T2 hypointensity is highly suggestive of RCC, while T2 hyperintensity has been described in 70% of RCC cases [8]. In this study, RCC brain MRI signal intensities were variable with T2 hypointensity in 45% and T2 hyperintensity in 38%, while 69% were T1 hyperintense. T1 hyperintensity is usually associated with a higher proteinaceous cyst content [31]. However, cyst content evaluated by intensity signal did not seem to be related either to presentation or outcome in our cohort.

Post-surgical outcome

Two-thirds of patients in this study had significant headache improvement after TSS, while visual field defects improved in all patients who demonstrated deficits prior surgery. In various series, headache recovery or improvement was noted in headaches ranging from 61–100% [1, 4, 14, 15, 18, 19, 32–34]. A recent meta-analysis found that two-thirds of patients will have headache improvement after RCC resection via TSS [35]. When distinguishing RCC size, some investigators have also observed that even patients with small RCC (<1 cm) who presented with headaches experienced improvement after resection [36].

In this cohort, all patients without visual changes underwent neurology evaluation and treatment for their headache; patients with medically-resistant headaches were offered surgery. As headache will not improve in all cases post-operatively, we suggest a pharmacological trial and other appropriate complimentary therapies for headache be attempted before considering surgery. Nevertheless, in those RCC patients with intractable headaches, surgery has a high success rate and should be considered.

The recurrence rate of surgically resected RCC in previous studies varies [4, 19, 20]. In large cohorts (53–155 patients) of patients who underwent surgical resection for symptomatic RCC, the radiological evidence of recurrence was noted as between 11–27% with a mean follow-up ranging between 2 and 8 years [1, 13, 17, 19, 21, 37–41]. In this study, RCC recurrence affected 25–30% of patients over a 4 year period, despite this, more than 50% of the patients in our group had surgical remission. Recurrence rate was similar in patients with gross total resection and in patients with residual RCC. Of note, the majority of RCC recurrences after TSS occur within 5–6 years. Therefore, close follow-up is recommended for at least 5 years after surgery [8, 42].

Previous studies have reported various predictors associated with a higher recurrence rate, including cyst size, visual field defects, squamous metaplasia, extent of cyst removal and residual cyst on postoperative MRI [8, 17, 19, 21, 42]. In this study, no factors were found to be associated with RCC recurrence, with the exception that headache at baseline was less frequent in the recurrent group and the size of recurrent cysts tended to be smaller. Since headache prevalence was high overall in both groups, the clinical significance of this finding is unclear.

Strengths and limitations

Study strengths include a large cohort of patients with a unified clinical and laboratory evaluation performed by one dedicated

neuroendocrinologist, a well-established clinical with biochemical and imaging follow-up protocol with neuropathologists, neuroradiologists and dedicated pituitary neurosurgeons.

Study limitations include a retrospective single-center study at a tertiary institution, with possible referral bias, and inherent patient selection bias related to the study population (surgically-resected RCC). As expected in a long term retrospective study, gaps in follow up imaging for various reasons (e.g., patient adherence, imaging performed at outside hospitals) are present for some patients and thus a precise recurrence time could not be determined, hampering us from determining the disease-free survival. Recurrence or progression might have been underestimated for some patients that have been lost to follow up or managed in an outside institution.

Conclusions

In this single center study of patients with RCC followed for a mean of 4 years, we have shown that headache was the presenting clinical complaint in RCC patients requiring TSS, even those patients with a small RCC. Headache as a presenting symptom could mark a more aggressive course. Symptomatic RCC is frequent in women, and surgery renders a high percentage of headache improvement. Adrenal insufficiency is the most frequent hormonal deficit in this patient population, which may not recover postoperatively, possibly associated with pericystic hypophysitis. Clinicians should cautiously screen patients with symptomatic RCC, regardless of lesion size for AI.

Accurate initial diagnosis, imaging and biochemical follow-up is recommended. Additional studies are required to highlight clinical differences and outcomes in symptomatic, surgically resected RCC vs. asymptomatic RCC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was waived in this institutional approved retrospective study.

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