Review

Rathke’s cleft cyst recurrence after transsphenoidal surgery: A meta-analysis of 1151 cases

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Abstract

Rathke’s cleft cysts (RCC) arise from the development of the Rathke’s cleft pouch. These commonly occurring cysts are typically asymptomatic, but sometimes present with headaches, endocrine dysfunction, and visual loss. Recurrence is common after either drainage or surgical removal. The purpose of this study was to review published outcomes for RCC management, and determine whether specific factors, including patient demographics, cyst pathology, radiologic parameters, or surgical techniques predispose to their recurrence. A systematic review of studies for RCC from 1990 to 2012 was conducted. Patients were identified using a Medline/PubMed search, and from the bibliographies of relevant articles obtained from the primary search. Relevant studies reporting recurrence rate were identified, and data were extracted regarding patient demographics, presenting symptoms, cyst characteristics, surgical treatment, and outcomes. A meta-analysis for recurrence rates was also performed. Twenty-eight journal articles comprising a total of 1151 RCC revealed an average follow-up of 38 months (range 16–79 months). In the studies reviewed, there was a relatively equal distribution of treatment approaches, with 35% subtotal resection, 33% complete resection, and 32% complete drainage with wall biopsy. The microsurgical transsphenoidal approach was found to have a higher recurrence rate (14% versus 8%) and new endocrine dysfunction rate (25% versus 10%) compared to the endoscopic approach. The data demonstrates a notable overall recurrence rate for RCC (12.5%). However, there appears to be no conclusive evidence that more aggressive resection of the cyst wall results in lower rates of recurrence.

Keywords: Rathke’s cleft cysts (RCC), recurrence, treatment, outcome, systematic review.

1. Introduction

Rathke’s cleft cysts (RCC) are benign sellar and/or suprasellar lesions thought to arise from the remnants of the Rathke pouch [1]. Rathke’s cleft describes the region that forms between the adenohypophysis and neurohypophysis during the third or fourth week of gestation. RCC arise when the Rathke’s cleft does not regress fully and remains patent [2].

The cyst wall is formed by an epithelial membrane, while the inside is filled with a mucinous, gelatinous, or caseous cystic fluid [3]. Although RCC are typically asymptomatic, some lesions exhibit growth and symptomatically compress surrounding neurovascular structures, requiring subsequent surgical therapy [4]. Common symptoms are visual and/or endocrine disturbances, [2] the most common symptom being headache [5]. For symptomatic RCC, surgical decompression through a transsphenoidal approach (microscopic or endoscopic) is commonly performed [1,6,7]. Complex cases of RCC that are very large or purely suprasellar with significant lateral extension may necessitate an open transcranial approach [4,8].

Successful decompression of the cyst commonly results in improved visual and endocrine function, as well as alleviation of headaches [9]. On the other hand, aggressive resection of the cyst wall has a notable rate of postoperative endocrine dysfunction, especially diabetes insipidus (DI) at a rate of 19% [2]. One of the primary features of RCC is their tendency to recur, making their optimal treatment and management strategy one that not only involves cyst decompression from neural structures, but also removal of the cyst wall to minimize recurrence.

There is no consensus over the most effective method of resection that alleviates symptoms and prevents recurrence while minimizing postoperative complications. Some feel that a complete drainage of cyst contents and biopsy of the cyst wall has the same efficacy as a gross total resection; however, the complete drainage of the cyst has a lower rate of postoperative disturbances [2,10]. In addition, there are other factors that reportedly may predict recurrence, including the presence of inflammation and squamous metaplasia in the cyst wall, MRI rim enhancement, use of packing material, and cyst location. In this report, we perform a systematic...
review and meta-analysis of the current literature on surgical management of RCC in order to determine particular factors that influence recurrence.

2. Materials and methods

2.1. Literature search strategy

A systematic review of published literature on patients with RCC was performed. The PubMed database was searched from 1990 to 2012 for “Rathke AND cleft AND cyst AND treatment”, and “features AND Rathke’s”. Titles were reviewed to identify studies that appeared to involve RCC. Abstracts were subsequently examined, followed by review of acquired full-text articles. Lastly, the references in the retrieved articles were examined for associated studies. Institutional Review Board approval was not required since this study qualified as “nonhuman subject research.”

2.2. Selection criteria and data management

All English-language studies reporting RCC were included. Articles were only included if they reported diagnosis, treatment, follow-up, and recurrence. Nonhuman, radiologic, cadaveric, anatomic, histologic, and molecular studies were excluded, as were sources with insufficient or unextractable data. Articles with unobtainable full text were also excluded. Assessment of study quality was performed, however there were few quality scales that could account for case series and case reports as they were developed for cohort, case-control, and randomized controlled studies [11,12]. Using the Quality Assessment Tool for Quantitative Studies (Effective Public Health Project 2007), it was determined that all of the studies included in this review were given the global rating of “weak” [13–15].

2.3. Data extraction

Two independent observers extracted data, and any discrepancies were discussed with inclusion into the database only occurring after consensus. Outcome measures extracted included demographic data (age, sex), symptoms (headache, endocrine dysfunction, visual deficit), cyst location (suprasellar, intrasellar, both), radiographic imaging, surgical approach (microsurgical transsphenoidal, endoscopic transsphenoidal, craniotomy), surgical technique (subtotal resection [STR], gross total resection [GTR], drainage and biopsy), complications, recurrence, and follow-up. Surgical techniques were defined as follows: drainage referred to emptying the cyst contents into the sphenoid sinus (via marsupialization, fenestration, simple drainage) and included a biopsy of the cyst wall; STR was a resection of the cyst wall beyond what was needed for a biopsy, but without removal of the entire cyst wall, along with total drainage of the cyst contents; and GTR was the removal of the entire cyst capsule and contents.

2.4. Data analysis

This study used StatsDirect (StatsDirect Ltd, Altrincham, UK) for meta-analysis, sensitivity/subgroup analysis, forest plots, and funnel plots. DerSimonian and Laird’s random-effects model was used to pool the recurrence rate from aggregated observational studies to form a weighted parameter estimate [16]. The random effects model was used because it assumes that the studies included are a sample of all potential studies, thus allowing between-study variability to be estimated [17]. Heterogeneity was determined using the $I^2$ statistic to assess for consistency. Visual inspection of the funnel plot along with Egger’s test was used to determine the presence of publication bias. Sensitivity analysis was performed by excluding each individual study to determine if there were any deviations in the overall estimate and by performing the same analysis after excluding studies with small sample size ($n < 10$). MedCalc (MedCalc Software, Ostend, Belgium) was used to create $2 \times 2$ contingency tables to perform chi-squared tests to determine differences in recurrence rates based on surgical treatment.
Table 2
Demographic data of patients with Rathke’s cleft cysts from studies included in the current review

<table>
<thead>
<tr>
<th>Location of cyst</th>
<th>Articles reporting</th>
<th>Patients, n</th>
<th>Total population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>93%</td>
<td>1151</td>
<td>30%</td>
</tr>
<tr>
<td>Intracranial with suprasellar extension</td>
<td>93%</td>
<td>1151</td>
<td>30%</td>
</tr>
<tr>
<td>Suprasellar</td>
<td>7%</td>
<td>37</td>
<td>3%</td>
</tr>
</tbody>
</table>

Table 3
Summary of outcome data from studies included in the current review

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Articles reporting</th>
<th>Patients</th>
<th>Weighted average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting symptom</td>
<td>Preoperative headache</td>
<td>86%</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td>Visual deficit</td>
<td>50%</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>Endocrine dysfunction</td>
<td>86%</td>
<td>89%</td>
</tr>
<tr>
<td>Location of cyst</td>
<td>Intracranial</td>
<td>61%</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td>Intracranial with suprasellar extension</td>
<td>61%</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td>Suprasellar</td>
<td>61%</td>
<td>46%</td>
</tr>
<tr>
<td></td>
<td>Cyst size (diameter)</td>
<td>43%</td>
<td>54%</td>
</tr>
<tr>
<td>Treatment</td>
<td>Transsphenoidal approach</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Open craniotomy</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Total drainage and wall biopsy</td>
<td>93%</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>Subtotal resection of cyst wall with complete drainage</td>
<td>93%</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>Gross total resection</td>
<td>93%</td>
<td>95%</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Average follow-up</td>
<td>86%</td>
<td>90%</td>
</tr>
</tbody>
</table>

3. Results

Searching the PubMed database using the keywords and manual bibliography search identified 157 studies (Fig. 1). Exclusion criteria included foreign language (n = 32), before the year 1990 (n = 22), nonhuman subjects (n = 15), no outcome or follow-up data (n = 8), no specific data on RCC characteristics (n = 7), case reports (n = 22), unextractable data (n = 4), insufficient data (n = 7), different diagnosis (n = 6), cannot locate (n = 5), and surgical technique paper without outcome data (n = 1). After applying the aforementioned criteria, 28 studies were included in the systematic review. Information on age, sex, location of cyst, associated symptoms, radiographic imaging, surgical technique, and recurrence was recorded if available. In total, the 28 studies included 1151 patients (Table 1).

Among the 28 studies, 93% reported sex, resulting in a total of 345 males and 769 females (2.2:1 female to male ratio) (Table 2). Since the majority of articles reported demographic data, symptoms, diagnostic imaging, cyst location, treatment approach, treatment technique, complications, and recurrence rate, the data are reported as weighted averages representing those articles that described each characteristic (Table 3). The most common symptoms within patients included headache (55%), endocrine dysfunction (46%), and visual deficit (34%). MRI was the most commonly used diagnostic imaging modality. Approximately 52% of RCC were intrasellar with suprasellar extension, 42% intrasellar, and 6% were purely suprasellar. Treatment approaches included the transsphenoidal approach (96%), whereas craniotomy was only used in 4% of patients. Of surgeries, 451 (39%) were reported to be microsurgical while 96 (8%) were reported as endoscopic (Table 4). In the 451 reported microsurgical transsphenoidal approaches, the weighted average of recurrence rate was 14% and the new postoperative endocrine dysfunction rate was 25% (Table 4). In the 96 reported endonasal endoscopic transsphenoidal approaches the weighted average of recurrence rate was 8% and the new postoperative dysfunction rate was 10% (Table 4). Treatment techniques included STR (35%), followed by GTR (33%), and drainage with biopsy (32%). Follow-up data for patients averaged 38 months (range 16–79 months). In articles only describing one treatment type the weighted average for recurrence rate was 19% for GTR (three studies, 30 patients, follow-up range 19–29 months), 9% for STR (eight studies, 229 patients, follow-up range 24–40 months), and 6% for drainage and biopsy (six studies, 138 patients, follow-up range 19–34 months). There was a significant difference in recurrence rate between GTR and drainage (p < 0.05, chi-squared test), whereas there was no difference in recurrence rate between STR and drainage (p > 0.05, chi-squared test).

To determine the overall recurrence rate of RCC we performed a meta-analysis of the 28 articles reporting recurrence rates, totaling 1151 patients. Sensitivity analysis showed no significant differences when meta-analysis was repeated following the exclusion of each article as well as those with 10 or fewer patients. The funnel plot demonstrated minimal asymmetry and Egger’s test was significant for publication bias (p < 0.05) (Fig. 2). Heterogeneity was considered high (I² = 58% [95% confidence interval (CI) = 32.8–71%]) necessitating a random-effects model for meta-analysis. The weighted estimate of recurrence was 12.5% (95% CI 0.095–0.158) using the random effects model (Fig. 3).

4. Discussion

4.1. Clinical information

RCC are benign sellar and/or suprasellar lesions. After pituitary adenomas, RCC are the most common lesion in the sellar region [3,18,19]. Incidental RCC are found in 11% to 33% of routine autopsies, as these lesions are rarely found to be symptomatic [20,21]. Symptomatic RCC occur twice as often in women than in men [2-1 in this study] and generally arise between the ages of 40 and 60 [22–25]. These lesions have been found to be on average 15 mm in size at time of diagnosis. The reported recurrence rate of RCC greatly varies in the literature from 0% to 30% [26] (12.8% in this analysis). The recommended postoperative follow-up period is at least a decade [24].

RCC have an epithelium-lined cyst capsule that varies in thickness and have been reported in varying colors from green to pink [27]. The epithelium typically has a simple structure but can be pseudostratified or stratified and encloses a mucinous, gelatinous, or caseous fluid interior [3,20,27]. However, the cyst lining is usually composed of a single layer of ciliated cuboidal or columnar epithelium, which may contain goblet cells [20,27,28]. RCC are a derivative of the Rathke pouch, which itself gives rise to the anterior lobe, pars intermedia, and pars tuberalis of the pituitary gland [3]. RCC occur when there is a persistence of the Rathke pouch that fails to close as it should early in fetal development [3]. The cysts can occur anywhere along the migration path of the Rathke pouch, but typically are found within the pituitary gland [3]. This study found the majority of RCC were intrasellar with suprasellar extension (52%), compared to 42% intrasellar and 6% suprasellar. RCC are most often found incidentally when imaging is performed in the region for unrelated symptomology, and usually appear as hyperintense MRI signal on both T1- and T2-weighted images [3].

RCC become symptomatic when they compress the surrounding area of the anterior visual pathways, pituitary stalk, and/or
hypothalamus which can cause headaches, hypopituitarism, or visual disturbances [3,21]. Reportedly symptomatic RCC may present with pituitary dysfunction (70%), visual disturbances (46–55%), and/or headaches (50%) [20,22,27,29]. In this analysis, the most commonly reported symptom was headache, followed by pituitary dysfunction, and visual changes. Headaches are typically frontal in location (57%) [27]. Pituitary dysfunctions usually manifest as amenorrhea–galactorrhea, panhypopituitarism, and DI [20,22,27,29]. Visual disturbances can include bitemporal hemianopia and decreased visual acuity associated with field defect [20,27].

Contemporary imaging techniques have made RCC a common incidental finding that rarely require more than conservative management [2,29–31]. Additionally, most asymptomatic RCC do not grow and may be managed with observation and serial MRI surveillance [2]. This analysis focused on patients with symptomatic RCC who were candidates for surgical intervention. To our knowledge, it is not entirely clear what mechanisms are behind the formation and/or development of RCC [2]. Hence a combination of factors must be considered before deciding on treatment options in order to reduce recurrence rates and the potential of reoperation.

Surgical treatment is the most effective route for symptomatic RCC and usually leads to the resolution of and improvement of headache, visual field defect, decreased visual acuity, hyperprolactinemia, and amenorrhea–galactorrhea syndrome [2,22,24]. Conversely, hypopituitarism and DI have not been shown to consistently improve [2,24].

4.2. Surgical management

For symptomatic RCC, the advised treatment is surgical decompression through a transsphenoidal approach, either microsurgical or endoscopic [1,6,7]. However, complex cases of RCC that are very large or purely suprasellar with lateral extension have been successfully approached by open craniotomy [4,8]. Our current study found that the overwhelming majority of surgeons utilized the transsphenoidal approach (96%), and only a small percentage used a craniotomy (4%). Within the
transsphenoidal approach, however, the endoscopic technique has gained popularity since it has the advantage of better tolerance and lower complication rate, while possessing good magnification and angled vision especially in the distal operative field [7]. In addition endoscopy allows for “freehand exploration” along with bimanual operation making it easier to assess the degree of resection as well as decrease morbidity [4]. This analysis interestingly demonstrated a lower recurrence rate and postoperative endocrine dysfunction rate in those treated using the endoscopic transsphenoidal approach (8% and 10%) compared to the microsurgical approach (14% and 25%). However, this finding must be taken in context, as this sub-group analysis represents a smaller subset of the overall study group, and that the microsurgical approach was performed five times more frequently than the endoscopic approach and occurred earlier in the study time frame. Further prospective studies must be performed to assess the relative benefit of the endoscopic approach compared to the microsurgical approach.

Fig. 3. Forest plot showing the aggregate patient data recurrence rate.
In addition to the treatment approach having an effect on recurrence rate and outcome, the surgical technique utilized may also vary to provide the best possible results. In an attempt to reduce recurrence, a more aggressive total resection is often chosen [2]. In this analysis, GTR took place in 33% of patients. However, in those studies that only reported GTR (three studies, 30 patients) the weighted average for recurrence rate was 19%, which differed significantly compared to the less aggressive approaches (p < 0.05). While this may appear to be greater than the recurrence rates after STR as well as drainage and biopsy, it must be pointed out that the majority of articles present a mix of treatment approaches. These 30 patients are therefore a gross underrepresentation of the GTR group, the second most common treatment approach utilized. Thus, the actual recurrence rate of this group is likely closer to the overall recurrence rate of 12.5% as this rate represents a larger number of GTR patients that were excluded from the smaller subset of studies that only reported a recurrence rate for GTR patients. In light of these findings, conclusions based on the statistical significance of differences between the GTR group and STR or drainage cannot be validated.

Compared to less radical resection, aggressive resection has a much higher rate of postoperative endocrine dysfunction [2,30]. The rate of permanent DI after the transsphenoidal approach has been reported between 3% and 19% and is associated with complete cyst wall resection [2,24,30]. Aho et al. reported a population of 118 patients, where 33 received aggressive radical resection (RR) and 85 received less radical resection (LRR) [2]. While both groups underwent successful GTR as confirmed by MRI (97% GTR), 42% of patients in the RR group experienced DI compared to 2.5% in the LRR group. This trend was also seen in terms of hypogonadism with RR leading to a 6% rate, and LRR resulting in a 2.5% rate [2]. In addition, the same study showed that RR did nothing to further reduce recurrence as compared to LRR (18% versus 21%, respectively) [2].

It has been reported that the treatment of choice of symptomatic RCC is the full evacuation of the contents and liberal opening (marsupialization) of the cyst wall [4,27]. Some suggest procedures more extensive than simple drainage should be approached with caution. Frank et al. state that extensive removal of the cyst wall should be carried out only where it is possible without causing additional pituitary damage [7]. Simple drainage and wall biopsy occurred in 32% of patients whereas STR of the cyst wall took place in 35% of patients treated in this study. The weighted recurrence rate in the subset of articles that described only one treatment methodology demonstrated that drainage and biopsy had a lower recurrence rate (6%) compared to STR (9%), however this was not statistically significant (p > 0.05). This may indicate that less aggressive approaches can be just as effective as more aggressive techniques. However, without controlling for size of cyst, anatomic location, and histologic features, any determination of efficacy of treatment approach is not currently possible.

There have been a variety of other techniques employed during removal of RCC to reduce its recurrence. Some, albeit without proof of increased efficacy, support the alcohol cauterization of the cyst wall [32]. Alcohol is used because it may help cauterize the wall of the cyst, which would aid in preventing recurrence [2]. This approach has been supported if no violation of the subarachnoid space is seen [2,22,32]. However, if the subarachnoid space has been perforated, the use of absolute alcohol for cauterization can have adverse consequences like permanent blindness [33].

4.3. Factors influencing recurrence

There are a variety of situations which appear to promote the recurrence of RCC, including the presence of squamous metaplasia, enhancement of the cyst wall on MRI [24] and the use of a fat and/or fascial graft [2,34]. Squamous metaplasia in the cyst wall is potentially the most important determinant factor for recurrence [2,24,29–31]. More aggressive RCC often are found with squamous metaplasia and suggest a closer relation to craniopharyngioma [1,2,4,8,30,31]. Similar to craniopharyngiomas, RCC may contain tyrosine-like or cholesterol crystals, macrophages, brown or gray inspissated fluid from an old hemorrhage, or thick, purulent and machine oil-like fluid [20,28,29].

It appears that some RCC are naturally more resilient and can present as panhypopituitarism, DI, progressive visual loss, or symptoms similar to meningitis or hypophysitis [4]. This subset of RCC has distinct imaging features of cyst wall rim enhancement that surrounds edema or inflammation, ossification, or hemorrhagic features [4]. This atypical RCC is often associated with multiple progressive clinical recurrences, which may require complete cyst wall resection even at the risk of developing pituitary dysfunction (Fig. 4) [4].

In addition to histological features and radiographic characteristics, there are iatrogenic causes that may predispose a patient to experiencing a recurrence of RCC. In a reported population of 29 patients where 22 had sellar packing, there were eight recurrences (28%), seven of which had packing of the sellar cavity (65% with abdominal fat) [34]. Some have postulated that packing the sellar cavity may prevent residual cyst wall epithelium from draining into the sphenoid sinus, thus trapping the cystic contents and promoting recurrence [34]. This finding has led some authors to recommend against packing the sellar defect and sellar floor reconstruction unless a cerebrospinal fluid leak is present [4,34]. In this study, there were two articles which concluded that the sellar packing was a significant factor for recurrence, [2,7] while five articles did not find sellar packing to be significant in their own series [4,6,30,31,35]. However, there is no conclusive data to suggest that packing the sella compared to marsupialization results in either greater or reduced recurrence.

An annual follow-up period of 5 years and additional follow-up for at least a decade after surgery is suggested to ensure there is no recurrence [2,4]. The articles included in this study had an average follow-up of at least 38 months ranging from 16 to 79 months, suggesting that further long term follow-up is likely to result in a higher recurrence rate than the finding of 12.5%.

4.4. Limitations

In any pooled data analysis, the major limitation that exists relates to the quality of available data in the literature. There were no randomized controlled analyses, the staple for a meta-analysis, and therefore the quality of the data is reduced with the inclusion of smaller case series. Using such heterogeneous sources of data introduces institutional, geographic, and selection biases. Also, although symptomatic RCC are relatively rare, the existence of these cysts is not. Consequently, there is significant publication bias present when reporting treatment and management of these entities. This was illustrated by the slightly asymmetric nature of the funnel plot and the significance of the Egger’s statistic.

In addition to methodological weaknesses in a systematic review, there were also limitations inherent to each published article. One of the major limitations of this study is the inclusion of publications with small sample sizes and those that do not include follow-up times that are greater than the natural course of recurrence of this disease [2]. Another major issue is the inconsistency in the reporting of data, especially with respect to the heterogeneity of scoring the totality of resection, differentiating treatment approaches (STR versus GTR versus drainage), method of transsphenoidal (endoscopic versus microscopic), reconstruction of sella.
packing versus no packing), and presence or absence of squamous metaplasia [31]. In addition, other factors that may influence recurrence such as cyst wall thickness have yet to be adequately described. We feel that future prospective controlled studies for treatment of symptomatic RCC are necessary. However, this systematic review is a new and relevant step toward further understanding of this disease process.

5. Conclusion

To our knowledge, this study describes the experience with the largest sample size of RCC. Headache, pituitary dysfunction, and visual dysfunction with a 2:1 female predilection is the most common presentation. Postoperative complications, such as pituitary dysfunction, can be kept to a minimum by using a less aggressive technique such as simple drainage. There was insufficient evidence to determine differences in recurrence rates between a more aggressive approach (GTR) and less aggressive approaches (STR and simple drainage with biopsy). In this analysis, the microsurgical approach resulted in a slightly higher recurrence rate and endocrine dysfunction rate compared to the endoscopic approach. However, due to the large differences in sample size between the two groups, further prospective studies must be performed to confirm these findings. The overall recurrence rate of RCC with current treatment methodologies is 12.5%.

Conflict of interest/disclosure

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References


Fig. 4. Sagittal (A) and coronal (B) gadolinium enhanced T1-weighted MRI of recurrent Rathke’s cleft cyst. Sagittal (C) and coronal (D) T2-weighted MRI of the same patient.


