The long-term recurrence of Rathke's cleft cysts as predicted by histology but not by surgical procedure

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OBJECTIVE Patients with symptomatic Rathke's cleft cysts (RCCs) managed by surgical treatment often experience recurrence. The authors attempted to clarify the outcome of surgically treated RCCs over a long-term follow-up period.

METHODS Ninety-one consecutive RCC patients with a follow-up period of more than 12 months (mean 80.2 months, range 12–297 months) were retrospectively studied. The authors examined the clinical features and postoperative course of patients who experienced a reaccumulation of cyst contents visible on MRI after the initial surgery, and they investigated data from the patients who underwent reoperation for symptomatic recurrent RCCs.

RESULTS Reaccumulation of cyst contents occurred in 36 patients (39.6%). In 34 of these patients, a reaccumulation occurred in the first 5 years after surgery. The initial cysts in these patients were most often large, with squamous metaplasia in the cyst walls. Thirteen patients (14.3%) with recurrent symptoms underwent a reoperation, and 10 of the 13 patients had a reaccumulation of RCCs within the 1st year after surgery. The reoperations were performed in the 1st year (61.5%) or several years later (23.1%). Patients were likely to initially have had a visual disturbance and the cyst walls likely included squamous metaplasia. However, no association was observed between the incidence of reaccumulation/reoperation of RCCs and the surgical procedure for RCCs.

CONCLUSIONS The reaccumulation rate of RCC is high in the long-term period, and it is associated with the histological findings but not with the surgical procedure. Long-term monitoring, for a period of at least 5 years, should therefore be conducted to identify and assess any RCC reaccumulation.

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KEY WORDS Rathke's cleft cysts; long-term outcome; transsphenoidal surgery; recurrence; reaccumulation; oncology

RATHKE's cleft cysts (RCCs) are cystic sellar and suprasellar lesions that are thought to originate from the remnants of Rathke's pouch. These common sellar lesions have been found in 3.7% of 1000 autopsies.¹³ They are usually asymptomatic;^{1,12,17} however, some RCCs can be symptomatic due to their mass effect and/or due to inflammatory injury of the surrounding structures.^{3,4,14}

Symptomatic RCCs are managed surgically by draining the cyst contents with or without biopsy or removal of the cyst wall. The removal of the entire cyst wall is associated with lower rates of cyst recurrence.^{2,8} It should

be noted that postoperative endocrine dysfunction is often caused by the aggressive removal of the cysts.^{1,2,5,16} Moreover, it has been reported that the extended resection of the cyst wall was not found to be associated with a decreased risk of relapse.^{1,5,10}

Recently, most surgical treatments for RCCs have involved the drainage of the cyst contents and the safe removal of as much of the capsule as possible, with or without marsupialization.^{14,17} However, there is no consensus as to which surgical procedures are the most effective for treating symptomatic RCCs.

ABBREVIATIONS RCC = Rathke's cleft cyst; TSS = transsphenoidal surgery.

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The reported recurrence rates of postoperative RCCs in patients who were surgically treated for RCC have ranged from 10% to 22%.^{1,5–9,11,15,16} The different findings reported in previous studies may be due to variations in the surgical procedures, follow-up periods, or follow-up protocols that were employed. The aim of the present study was to clarify the recurrence rate of RCCs in patients who were treated surgically (with uniform surgical procedures) and in those who underwent postoperative routine MRI for a long-term follow-up period (mean 80.2 months), and also to assess the factors that predict the recurrence of RCCs.

Methods

Patient Population

We retrospectively studied 91 consecutive patients who were diagnosed with RCC based on MRI and intraoperative findings at Hiroshima University Hospital between 1986 and 2014. The mean age of the 36 male and 55 female patients at the time of operation was 53.0 years (range 12–81 years). The minimum follow-up period for inclusion in this study was 12 months.

Preoperative Evaluation

All patients underwent physical and ophthalmological examinations, an endocrinological workup, and MRI, and their detailed general and neurological histories were recorded. Their anterior pituitary function was evaluated by their response to induced hypoglycemia and/or to the administration of corticotropin-releasing hormone (100 µg), thyrotropin-releasing hormone (500 µg), luteinizing hormone-releasing hormone (100 µg), and/or arginine (30 g).

Surgical Procedures

Prior to 1995, microscopic transsphenoidal surgery (TSS) was performed via the sublabial transsphenoidal approach. Endoscopic assistance for TSS was introduced in 1995, and a completely endoscopic procedure was adopted in 2010. The sublabial transsphenoidal approach shifted

to the endonasal transsphenoidal approach in 2002. The surgical procedures included drainage of the cyst contents and a biopsy of the cyst wall with or without a stoma between the cyst and the suprasellar cistern or sphenoid sinus. Prior to 2005, simple cyst drainage and a biopsy were performed. In cases after 2005, an attempt was made to create a stoma of the suprasellar cistern with a fat graft placed inside the cyst to prevent CSF leakage. The sellar floor was reconstructed using autologous bone from the vomer. In the initial operations, we did not attempt the removal of the entire cyst wall and did not irrigate the cyst cavity using absolute ethanol. Six of the patients in the present series first underwent transcranial surgeries for RCCs.

Pathological Tissue Analysis

The tissue specimens obtained during these operations were fixed in formalin, embedded in paraffin, sectioned, and stained with H & E. A histopathological diagnosis of RCC was established in 79 patients. A histopathological diagnosis was not obtained in the other 12 patients, either because the biopsy failed ($n = 9$) or because a biopsy was not performed ($n = 3$). In those 12 patients, we diagnosed RCC based on MRI and intraoperative findings and on the patients' postoperative courses.

Treatment Follow-Up and the Definition of Reaccumulation and Reoperation

The mean follow-up period was 80.2 months (median 70 months, range 12–297 months). All patients generally underwent postoperative MRI at 3 months after surgery and annually thereafter (even patients who were asymptomatic with no reaccumulation of the cyst contents). We defined reaccumulation as the enlargement (even a slight enlargement) of the reduced or resolved postoperative cyst cavity on sagittal MR images (Fig. 1). Asymptomatic patients exhibiting the reaccumulation of cyst contents were followed up with MRI performed every 3 to 6 months. Reoperation was performed in patients who again devel-

FIG. 1. Sagittal T1-weighted MR images obtained in a 15-year-old boy who presented with a chronic headache. **A:** Preoperative image showing a high-intensity cyst. **B:** Image obtained 3 months after undergoing surgery for drainage and biopsy showing that the cyst has disappeared. **C:** Image obtained 6 months after surgery showing the reaccumulation of the cyst contents. **D:** Image obtained 30 months after surgery showing a slightly enlarged cyst.

FIG. 2. Sagittal T1-weighted MR images obtained in a 32-year-old woman who presented with a chronic headache and amenorrhea. **A:** Preoperative image showing an isointense to high-intensity cyst. **B:** Gd-enhanced image obtained 6 days after surgery for drainage and biopsy showing that the cyst has disappeared. **C:** Image obtained 2 months after surgery showing the reaccumulation of the cyst contents. The patient underwent reoperation due to recurrent symptoms.

opened symptoms due to RCC reaccumulation after the initial surgery (Fig. 2). The incidence of reoperation reflects the incidence of symptomatic reaccumulation of RCC in this study.

Statistical Analysis

All statistical analyses were performed using the software package SPSS 16.0 J for Windows (SPSS Inc.). The Mann-Whitney U-test and Fisher's exact test were used for comparisons. The values are expressed as medians. A p value of < 0.05 was considered to be statistically significant.

Results

The Incidence and Timing of Reaccumulation and Reoperation

A reaccumulation of the cyst contents was observed

in the postoperative MRI examinations of 36 patients (39.6%) (Fig. 3). In most patients, this reaccumulation occurred in the first 5 years after surgery ($n = 34$, 94.4%), and such a reaccumulation could even be found more than 10 years after surgery (Fig. 4). Thirteen patients with recurrent symptoms underwent a reoperation. In most of the patients who underwent a reoperation, the reaccumulation of cyst contents occurred in the 1st year after surgery ($n = 10$, 76.9%). However, the timing of the reoperations was bimodal: either during the 1st year after surgery ($n = 8$, 61.5%) or several years after the initial surgery ($n = 3$, 23.1%) (Fig. 5). No patients required a reoperation after 10 years of follow-up.

The Clinical Features of Patients With Reaccumulation

The details of the clinical features at the initial surgery of patients with a reaccumulation are shown in Table 1. The patients with a reaccumulation had a larger initial cyst

FIG. 3. Schematic showing the outcomes of 91 patients who underwent surgical treatment.

TABLE 1. The clinical features at the initial surgery in patients with reaccumulation of cyst contents and those who underwent reoperation*

Characteristic	Total Cases (n = 91)	Reaccumulation			Reop		
		No (n = 55)	Yes (n = 36)	p Value	No (n = 78)	Yes† (n = 13)	p Value
Age in years, median	53.0	54.0	48.0	0.2944	54.0	48.0	0.3763
M:F ratio	36/55	25/30	11/25	0.1911	32/46	4/9	0.5544
Symptoms							
Visual disturbance	39 (42.9)	21 (38.2)	18 (50.0)	0.2866	29 (37.2)	10 (76.9)	0.0131
Headache	29 (31.9)	17 (30.9)	12 (33.3)	0.8218	27 (34.6)	2 (15.4)	0.2125
Hypopituitarism, hyperprolactinemia	16 (17.6)	11 (20.0)	5 (13.9)	0.5775	13 (16.7)	3 (23.1)	0.6934
Diabetes insipidus	15 (16.5)	9 (16.4)	6 (16.7)	>0.99	12 (15.4)	3 (23.1)	0.4436
None	5 (5.5)	3 (5.5)	2 (5.6)	>0.99	4 (5.3)	1 (7.7)	0.5460
APG dysfunction	64 (70.3)	36 (65.5)	28 (77.8)	0.2464	53 (67.9)	11 (84.6)	0.3304
T1-weighted MRI							
High intensity	37 (40.7)	20 (36.4)	17 (47.2)		31 (39.7)	6 (46.2)	
Isointense	29 (31.9)	21 (38.2)	8 (22.2)		24 (30.8)	5 (38.5)	
Low intensity	25 (27.5)	14 (25.5)	11 (30.6)	0.2758	23 (29.5)	2 (15.4)	0.5694
T2-weighted MRI							
High intensity	57 (62.6)	35 (63.6)	22 (61.1)		49 (62.8)	8 (61.5)	
Isointense	19 (20.9)	10 (18.2)	9 (25.0)		15 (19.2)	4 (30.8)	
Low intensity	15 (16.5)	10 (18.2)	5 (13.9)	0.6873	14 (17.9)	1 (7.7)	0.4905
Nodule	17 (18.7)	8 (14.5)	9 (40.0)	0.2733	14 (17.9)	3 (23.1)	0.7035
Cyst size, median in mm	18.0	15.0	18.0	0.0432	18.0	19.0	0.1677
Operative procedures							
Use of fat graft	55 (60.4)	33 (60.0)	22 (61.1)	>0.99	47 (60.3)	8 (61.5)	>0.99
Marsupialization							
Suprasellar cistern	37 (40.7)	21 (38.2)	16 (44.4)		32 (41.0)	5 (38.5)	
Sphenoidal sinus	6 (6.6)	4 (7.3)	2 (5.6)		5 (6.4)	1 (7.7)	
None	48 (52.7)	30 (54.5)	18 (55.6)	0.8218	41 (52.6)	7 (53.8)	0.9757
Pathological findings							
Single	60 (65.9)	40 (72.7)	20 (55.6)		56 (71.8)	4 (30.8)	
Multiple	10 (11.0)	4 (7.3)	6 (16.7)		7 (9.0)	3 (23.1)	
Squamous metaplasia	7 (7.7)	1 (1.8)	6 (16.7)	0.0130	2 (2.6)	5 (38.5)	<0.0001
Unknown	14	10	4		13	1	

APG = anterior pituitary gland.

* Values are number (%) of patients unless otherwise indicated.

† Reoperation was performed in patients with symptomatic reaccumulation of RCC.

size ($p = 0.0432$). On pathological examination, their cyst walls were significantly more frequently found to contain multiple epithelial layers and squamous metaplasia ($p = 0.0130$). On the other hand, there were no significant differences in the clinical symptoms, endocrinological examinations, or the operative procedures of the patients with a reaccumulation.

The Clinical Features of Patients Who Underwent Reoperation

The detailed clinical features at the initial surgery in patients who underwent reoperation are described in Table 1. The patients who underwent reoperation were likely to have initially had a visual disturbance ($p = 0.0131$), and their cyst walls were significantly more frequently found to contain multiple epithelial layers and squamous metaplasia on pathological examination ($p < 0.0001$). There

were no significant differences in the endocrinological examinations, MRI findings, or the operative procedures in the patients who underwent reoperation compared with those who did not undergo reoperation.

Discussion

The reaccumulation rates of postoperative RCCs have been shown to vary in surgically treated patients (Table 2).^{1,2,5,6,8,9,11,15,16,18} We observed a high incidence of reaccumulation after surgical treatment. The variations in the reaccumulation rates in previous reports are considered to be due to a number of reasons. Firstly, the surgical procedures of the past reports were not uniform. The total removal of the cyst wall is an entirely different procedure from the drainage and/or the biopsy of an RCC. The total removal of the cyst would theoretically ensure that no reac-

FIG. 4. Graph showing that reaccumulation occurred in the first 60 months after surgery in 34 (94.4%) of the 36 patients in whom MRI demonstrated a reaccumulation of the cyst contents. The latest case of reaccumulation occurred 152 months after surgery.

cumulation of the cyst occurs, and it could thereby reduce the reaccumulation rate. Secondly, the follow-up protocols were not clarified in most reports. To detect the asymptomatic reaccumulation of an RCC, all patients must be monitored with routine postoperative MRI examinations. Regular MRI check-ups can increase the rate at which reaccumulation is observed. Thirdly, a long-term monitoring period is needed to assess the reaccumulation rate of RCCs.^{14,15} In the present study, the gradual increase in the reaccumulation rate of RCCs in the first 5 years after surgery implies that a follow-up period of at least 5 years is needed. With a short-term follow-up period investigators have the potential to underestimate the reaccumulation

FIG. 5. Graph showing the bimodal timing of reoperation in the 13 patients with recurrent symptoms. Reoperations occurred either during the 1st year after the initial surgery ($n = 8$, 61.5%) or several years after the initial surgery ($n = 3$, 23.1%). No patients required reoperations after 10 years of follow-up.

TABLE 2. The incidence of reaccumulation of cyst contents and reoperation in past reports

Authors & Year	No. of Pts	Reaccumulation (%)	Reop (%)	Mean FU (mos)
Kim et al., 2004	53	NA	11.3	31
Benveniste et al., 2004	62	NA	12.9	28
Aho et al., 2005	118	17.8	10.2	>60
Potts et al., 2011	151	11.3	7.9	30
Wait et al., 2010	73	11.0	5.5	27
Higgins et al., 2011	61	18.0	13.1	60.5
Jahangiri et al., 2011	147	12.2	NA	23*
Lillehei et al., 2011	75	10.7	NA	3
Trifanescu et al., 2011	32	21.9	18.8	48
Zhong et al., 2012	41	14.6	4.9	16
Present study	91	39.6	14.3	80.2

FU = follow-up; NA = not available; Pts = patients.

* Value is the median.

rate of RCCs. We, therefore, assume that the actual reaccumulation rate of RCCs reported in a long-term period would be higher than that reported in a short-term period.

The factors associated with a higher rate of reaccumulation have been discussed and include a purely suprasellar location, large initial cyst size, enhancement of the lesion on MRI, the use of a fat graft in the cyst cavity, intraoperative CSF leakage, a residual cyst observed on postoperative MRI, and inflammation and reactive squamous metaplasia in the cyst wall.^{1,2,4,8,9,11,14,16,18} We showed that the predicting factors for the reaccumulation and reoperation of RCCs were clinical visual field defects, large initial cyst size, and squamous metaplasia. Above all, squamous metaplasia in the cyst wall might be the most important factor associated with the reaccumulation and reoperation of RCCs. Operative procedures were not found to affect the incidence of reaccumulation or the reoperation rate.

We suggest that there are 3 methods for preventing the reaccumulation of RCCs: completely removing the cyst wall, stopping the secretion of mucus from the epithelial cells, and making a permanent marsupialization of the RCC. When surgical procedures lacking these 3 methods are conducted, the reaccumulation of RCCs can be expected to occur due to the mucus-secreting cells that remain. The extended resection of the cyst wall is not conducted in the initial surgery for RCCs due to the high incidence of postoperative endocrine dysfunction,^{1,2,5,16} and the methods for preventing the secretion of mucus from the epithelial cells have not been established (the effectiveness of absolute ethanol has not been certified).⁹ We attempted to create a permanent stoma between the RCC and the suprasellar cistern; however, the procedures could not reduce the reaccumulation rate of RCCs in the long-term period. Our results showed that it was technically difficult to make a permanent stoma for RCCs and suggest that while the operative procedures might have an effect on the short-term reaccumulation rate of RCCs, the difference might disappear over the long-term period.

Conclusions

The presence of squamous metaplasia in the cyst wall is the most important factor associated with the reaccumulation and reoperation rates of RCCs that cannot be reduced using surgical devices. As the long-term rate of reaccumulation of RCC is high, a monitoring period of at least 5 years should be implemented to assess the degree of reaccumulation of RCCs after the initial surgery.

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Disclosures

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

Author Contributions

Conception and design: Kinoshita, Tominaga. Acquisition of data: Kinoshita, Tominaga, Usui, Arita, Sakoguchi. Analysis and interpretation of data: Kinoshita, Tominaga. Drafting the article: Kinoshita. Critically revising the article: Tominaga, Sugiyama, Kurisu. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kinoshita. Statistical analysis: Kinoshita. Administrative/technical/material support: Tominaga, Sugiyama, Kurisu. Study supervision: Tominaga, Kurisu.

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