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Natural history and surgical outcome of Rathke's cleft cysts—A study from the Swedish Pituitary Registry

Maria Petersson[1] | Katarina Berinder[1] | Britt Eden Engström[2] | Erika Tsatsaris[2] | Bertil Ekman[3] | Jeanette Wahlberg[3,4] | Pia Burman[5] | Henrik Borg[6] | Peter Siesjö[7] | Per Dahlqvist[8] | Anna-Karin Åkerman[4] | Oskar Ragnarsson[9] | Martin Olsson[10] | Petter Förander[10] | Sophie Bensing[1] | Charlotte Höybye[1]

[1]Department of Molecular Medicine and Surgery, Karolinska Institutet and Department of Endocrinology, Karolinska University Hospital, Stockholm, Sweden

[2]Department of Medical Sciences, Endocrinology and Mineral Metabolism, Uppsala University and Uppsala University Hospital, Uppsala, Sweden

[3]Department of Endocrinology in Linköping and Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

[4]Department of Internal Medicine, School of Health and Medical Sciences, Örebro University, Örebro, Sweden

[5]Department of Endocrinology, Skåne University Hospital, University of Lund, Malmö, Sweden

[6]Department of Endocrinology, Skåne University Hospital, University of Lund, Lund, Sweden

[7]Department of Neurosurgery, Skåne University Hospital, University of Lund, Lund, Sweden

[8]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

[9]Department of Internal Medicine and Clinical Nutrition, Institute of Medicine at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[10]Department of Neurosurgery, Karolinska University Hospital, Stockholm, Sweden

Correspondence
Maria Petersson, Department of Endocrinology, Karolinska University Hospital, SE-17176 Stockholm, Sweden.
Email: maria.petersson@ki.se

Abstract

Objective: Rathke's cleft cysts are benign, embryological remnants in the pituitary gland. The majority of them are small and asymptomatic but a few may become large, and cause mass effects, pituitary hormone deficiencies and visual impairment. Recommendations for the follow-up of Rathke's cleft cysts vary since data on the natural history are sparse.

Patients and Design: Data at diagnosis and at 1, 5 and 10 years for patients with a Rathke's cleft cyst (434 at diagnosis, 317 females) were retrieved from the Swedish Pituitary Registry. Cysts ≤3 mm in diameter were excluded from the study.

Measurements: Data included demographics, cyst size, pituitary function, visual defects and surgery.

Results: The mean age at diagnosis was 45 years. In patients with cysts <10 mm in diameter (n = 204) 2.9% had pituitary hormone deficiencies and 2% had visual field impairments. Cyst size did not progress during the 5 years. Cysts with a diameter of ≥10 mm that were not operated (n = 174) decreased in size over the years (p < .01).

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Pituitary hormone deficiencies and visual impairments were more frequent (18% and 5.7%, respectively) but were stable over time. Transphenoidal surgery was performed in 56 patients of whom 51 underwent surgery before the 1-year follow-up. The mean cyst diameter at diagnosis was 18 mm (range: 9—30 mm), 36% had pituitary hormone deficiency, 45% had visual field defects and 20% had impaired visual acuity. One year after surgery 60% had no cyst remnants, 50% had a pituitary deficiency, 26% had visual field defects and 12% had impaired visual acuity. No major changes were observed after 5 years. Twelve of the operated patients had a follow-up at 10 years, in eight the cyst remnants or recurrences increased in size over time ($p < .05$).

Conclusions: Rathke's cleft cysts with a size less than 10 mm rarely grow and our results indicate that radiological follow-up can be restricted to 5 years. In contrast, progression of postoperative remnants or recurrent cysts is more likely and require long-term follow-up.

KEYWORDS

cyst size, hypopituitarism, pituitary, Rathke's cleft cyst, transphenoidal surgery, visual impairment

1 | INTRODUCTION

Benign tumours and cysts in the pituitary are common, and Rathke's cleft cysts are the most frequently reported cysts. The incidence of a Rathke's cleft cyst at autopsy has been reported to range between 5% and 33%,[1,2,3] with a peak incidence between the age of 30–50 years.[4] Some studies indicate a female preponderance probably because of an earlier detection due to irregular or discontinued menstrual cycles caused by gonadotrophin deficiency.[3,4]

Rathke's cleft cysts are benign remnants from embryology when the adenohypophysis (emanating from the Rathke's pouch and the ectoderm) and the neurohypophysis (from the neuroectoderm) migrate from their separate origins to form the pituitary. The cysts are usually small and asymptomatic and are often incidental findings on magnetic resonance imaging (MRI) or computed tomography performed for other reasons such as trauma, headache or vertigo. Small Rathke's cleft cysts located in the median lobe of the pituitary are also called pars intermedia cysts. These cysts are often so small, just a few millimetres, that follow up not is indicated. However, there are large variations in the size of Rathke's cleft cysts from a few millimetres to several centimetres. The largest Rathke's cleft cysts that have been reported are 5 cm in diameter.[3,4]

A large Rathke's cleft cyst may compress surrounding structures, resulting in visual disturbances, headaches and/or deficiencies of pituitary hormones. Thus, depending on cyst size and localisation, the reported symptoms vary significantly. The most common presenting symptoms include headache (33%–81%), visual disturbance (12%–58%) and pituitary hormone deficiencies with one or more axes affected (19%–81%).[4-10] Large symptomatic Rathke's cleft cysts, especially if they cause visual symptoms, are usually operated on.

The aim of the present study was to quantify the potential changes in cyst size over time, the number of patients with pituitary deficiencies, and visual impairments in a large national cohort of patients with Rathke's cleft cysts registered in the Swedish Pituitary Registry. Additional aims were to report the frequency and outcome of surgery.

2 | METHODS

2.1 | Study design

This study reports data retrieved from the Swedish Pituitary Registry. The Swedish Pituitary Registry was established in 1991 and collects information on basic demography, clinical and hormonal findings, treatment and outcome of patients with pituitary adenoma, craniopharyngeoma and Rathke's cleft cyst. The data are validated continuously by local monitors.

In the present study, data on patients with Rathke's cleft cysts from the registry were collected. The diagnosis was based on radiological identification of a Rathke's cleft cyst on MRI. Data of age, sex and binary registration of pituitary insufficiency, impairment of visual acuity and visual fields (179 of the patients were reviewed by an ophthalmologist) and surgery were retrieved at diagnosis and after 1 (data between 0.5 and <2.5 years), 5 (data between 2.5 and <7.5 years) and 10 years (data between 7.5 and <12.5 years).

Adequacy of the pituitary hormone axes were assessed by local centres according to national protocols and diagnostic criteria. The diagnosis of growth hormone (GH) status were according to

international guidelines and therefore did not necessarily involve a GH stimulation test in patients with more than three other pituitary hormone deficiencies.

Since the total cohort of patients with Rathke's cleft cysts was very inhomogeneous and only five of the operated patients were undergoing surgery after the 1-year follow-up, data for the follow-ups were divided into nonoperated (<10 and ≥10 mm) and operated patients. Nonoperated patients with 10 years follow-up were also analysed separately.

Patients with cysts ≤3 mm were excluded together with nine patients erroneously diagnosed with a Rathke's cleft cyst (four craniopharyngeomas, one nonfunctioning adenoma, three arachnoid cysts and one with an unclear diagnosis).

2.2 | Ethics

The Swedish Pituitary Registry is approved by the Ethics Committee at the Karolinska Institute, 2003 (Dnr 515/03) and 2012 (Dnr 915-32).

2.3 | Statistical methods

Data are presented as mean ± SD. A possible difference in age and cyst size between genders was evaluated using the Student's *t*-test.

Changes in cyst volume and diameter over time were analysed with a one-way analysis of variance (ANOVA) and an ANOVA for repeated measurements followed by paired Student's *t*-test with Bonferroni correction. Statistical values of $p < .05$ were considered as significant.

3 | RESULTS

3.1 | Total cohort of patients with Rathke's cleft cysts

In total 434 patients (317 females and 117 males) with Rathke's cleft cysts were identified in the registry. Their mean age was 45 years and the mean cyst volume was 730 mm^3 with a mean diameter of 11 mm. No differences were found between males and females.

One or more pituitary deficiencies were observed in 38 females and 20 males. Gonadotropin deficiency was the most common hormonal deficiency and it was more frequently reported in males. Thyrotropin (TSH) deficiency was the second most common deficiency (Table 1). Impaired visual fields and visual acuity were reported in 9.0% and 3.5%, respectively. Of note, half of the females with visual field defects also had impaired visual acuity. This was not observed in the males (Table 1).

3.2 | Rathke's cleft cysts <10 mm, not operated

At diagnosis 204 patients (47%) (142 females and 62 males) had a Rathke's cleft cyst of <10 mm. The cysts had a mean volume of 107 mm^3 and a mean diameter of 6 mm. No differences were found between males and females. The mean cyst size was unchanged between the baseline and 5 years follow-up. Only one of the cysts became larger than 10 mm (diameter 8 mm at diagnosis, and 11 and 10 mm at 1 and 5 years, respectively).

The rate of patients with pituitary deficiencies increased from 2.9% at diagnosis to 7% at the 5-year follow-up, mainly due to an increase in patients with gonadotropin deficiency. Impairments of

TABLE 1 Data at diagnosis for all patients with a Rathke's cleft cyst registered in the Swedish Pituitary Registry

	Total	Females	Males
Number	434	317	117
Age (years)	45.2 ± 17.0	44.1 ± 17.1 (19–89)	48.1 ± SD 16.4 (19–88)
Diameter (mm)	10.7 ± 5.62	10.9 ± 5.66	10.2 ± 5.51
Volume (mm^3)	730 ± 1499	724 ± 1568	746 ± 1300
Any pituitary deficiency	58/438 434 (13%)	38/317 (12%)	20/117 (17%)
GH-def	15/434 (3.5%)	8/317 (2.5%)	7/117 (6.0%)
ACTH-def	32/434 (7.4%)	23/317 (7.3%)	9/117 (7.7%)
TSH-def	38/434 (8.8%)	24/317 (7.6%)	14/117 (12%)
LH/FSH-def	40/434 (9.2%)	19/317 (6.0%)	21/117 (18%)
ADH-def	8/434 (1.8%)	5/317 (1.6%)	3/117 (2.6%)
Visual field defects[a]	39/434 (9.0%)	27/317 (8.5%)	12/117 (10%)
Visual acuity impairment[a]	15/434 (3.5%)	14/317 (4.4%)	1/117 (0.8%)

Note: Data are shown as mean ± SD. Range for age within parenthesis.

Abbreviations: ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyrotropin.

[a]Number based on the total cohort. A total of 179 patients were examined by an ophthalmologist.

TABLE 2 Data at diagnosis, and at the 1- and 5-year follow-up of patients with a Rathke's cleft cyst with a diameter <10 mm at diagnosis

	Diagnosis	1 Year	5 Years
Number	204	121	71
Age (years)	42.9 ± 16.1 (19–85)		
Diameter (mm)[a]	6.4 ± 1.67	6.0 ± 2.18	6.4 ± 2.31
Volume (mm^3)[a]	107 ± 87.1	101 ± 90.5	124 ± 105
Any pituitary deficiency	6/204 (2.9%)	4/121 (3.3%)	5/71 (7.0%)
GH-def	1/204 (0.5%)	0%	0%
ACTH-def	2/204 (1.0%)	0%	1/71 (1.4%)
TSH-def	4/204 (2.0%)	0%	1/71 (1.4%)
LH/FSH-def	7/204 (3.4%)	3/121 (2.5%)	4/71 (5.6%)
ADH-def	5/204 (2.5%)	1/121 (0.8%)	1/71 (1.4%)
Visual field defects	4/204 (2.0%)	1/121 (0.8%)	1/71 (1.4%)
Visual acuity impairment	1/204 (0.5%)	0%	0%

Note: Data are shown as mean ± SD. Range for age within parenthesis.

Abbreviations: ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; ANOVA, analysis of variance; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyrotropin.

[a]Cyst size (diameter and volume) was analysed with one-way ANOVA for data between years (diameter: $F = 1.87$, $p = .16$, volume: $F = 1.33$, $p = .27$) and with ANOVA for repeated measurement of data within patients ($n = 47$) (diameter: $F = 1.67$, $p = .19$, volume: $F = 0.91$, $p = .41$).

visual field and visual acuity were rare at diagnosis (2% and 0.5%) and remained unchanged during follow-up (1.4% and 0%; Table 2).

3.3 | Rathke's cleft cysts ≥10 mm, not operated

At diagnosis 174 patients (129 females and 45 males) had cysts ≥10 mm, with a mean volume of 950 mm^3 and a mean diameter of 13.5 mm. No differences were found between males and females. The mean cyst size decreased over time and was significant when compared within the individual patient ($p < .01$). At the fifth year follow-up 48% of the cysts had decreased in size whereas 15% had increased in size. The mean cyst volume was 625 mm^3 and the mean diameter 11.8 mm (Table 3).

In this subgroup, 18% (31 of 174) had pituitary hormone deficiency. Impairments of visual field and visual acuity were present in 5.7% and 1.7%, respectively at diagnosis. The number of patients with pituitary deficiencies, impaired visual fields and visual acuity was stable during follow-up (Table 3).

3.4 | Ten years follow up of patients with Rathke's cleft cyst, not operated

Follow-up at both 5 and 10 years was available for 24 patients of the patients described above (19 females and 5 males; for detailed information see Table S1). Cysts decreased significantly during the follow-up period (Figure 1). The diameter at diagnosis was 12.2 ± 6.56 mm, at 5 years 10.4 ± 4.79 mm and at 10 years

TABLE 3 Patients with a Rathke's cleft cyst with a diameter ≥10 mm at diagnosis and at the 1- and 5-year follow-up

	Diagnosis	1 Year	5 Years
Number	174	102	73
Age (years)	46.1 ± 18.0 (19–89)		
Diameter (mm)[a]	13.5 ± 4.19	12.2 ± SD 4.61	11.8 ± SD 4.58
Volume (mm^3)[a]	950 ± 1287	759 ± 1105	625 ± 695
Any pituitary deficiency	31/174 (18%)	20/102 (20%)	16/73 (22%)
GH-def	7/174 (4.0%)	4/102 (3.9%)	3/73 (4.1%)
ACTH-def	15/174 (8.6%)	9/102 (8.8%)	7/73 (9.6%)
TSH-def	18/174 (10%)	11/102 (11%)	7/73 (9.6%)
LH/FSH-def	19/174 (11%)	11/102 (11%)	13/73 (18%)
ADH-def	1/174 (0.6%)	2/102 (2.0%)	1/73 (1.4%)
Visual field defects	10/174 (5.7%)	4/102 (3.9%)	4/73 (5.5%)
Visual acuity impairment	3/174 (1.7%)	2/102 (2.0%)	1/73 (1.4%)

Note: Data are shown as mean ± SD. Range for age within parenthesis.

Abbreviations: ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; ANOVA, analysis of variance; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyrotropin.

[a]Cyst size (diameter and volume) was analysed with one-way ANOVA for data between years (diameter: $F = 2.88$, $p = .063$, volume: $F = 2.35$, $p = .096$) and with ANOVA for repeated measurement of data within patients ($n = 46$) (diameter: $F = 13.4$, $p < .0001$, volume: $F = 5.30$, $p = .0067$).

9.0 ± 4.99 mm (F = 5.63, p = .0065). Corresponding cyst volumes were 848 ± 1257, 516 ± 632 and 410 ± 578 mm^3 (F = 3.71, p = .032).

Three patients had pituitary deficiency at the time of diagnosis (one deficiency of gonadotrophins and two panhypopiutiarism). One of the patients with panhypopitutarism at the time of diagnosis did not have any deficiency at 5 and 10 years, while the pituitary deficiency was unchanged in the other two. One patient with normal pituitary function at diagnosis developed a gonadotrophin deficiency.

None of the patients had a visual disturbance.

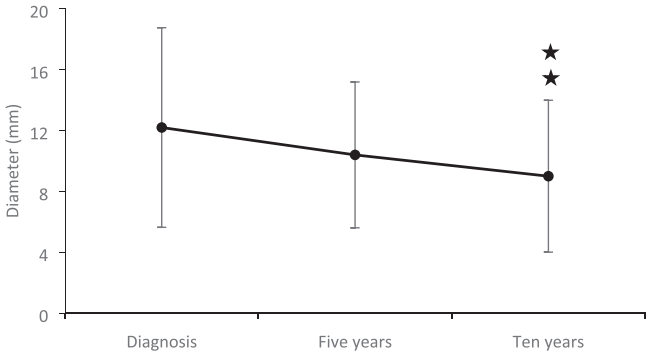

FIGURE 1 Diameter of the Rathke's cleft cysts in the 24 patients (19 females and 5 males) that had a follow-up at both 5 and 10 years. Data are presented as means ± SD. Statistical analysis was performed with ANOVA for repeated measurements followed by a Student's t-test for paired observations and by Bonferroni correction. F = 5.63, p = .0065. ANOVA, analysis of variance. $^{**}p < .01$, compared to the diameter at diagnosis

3.5 | Surgery and outcome

Fifty-six patients underwent transsphenoidal surgery (46 females and 10 males). The mean cyst size was 18 ± 6.12 mm with a volume of 2315 ± 2881 mm^3. Data at diagnosis for these 56 patients are shown in Table S2. Five of the 56 patients were not included in the main analysis of operated patients (four females and one male that were operated later than the 1-year follow-up).

For the 51 patients who underwent surgery before the 1-year follow-up, the mean cyst size was 18 ± 6.19 mm in diameter with a volume of 2473 ± 2972 mm^3 (Table 4). Two of the operated patients had a cyst <10 mm (one had visual field impairments, but why the other was operated is unknown).

There were no significant sex differences in cyst size. Despite this, the two largest cysts, which were 30 and 35 mm in diameter, were found in females, and interestingly one of them had no pituitary deficiency or impairment of vision or visual fields. After surgery, 30 patients had no visible remnant of the cyst, whereas 19 patients still had a visible cyst (data for two patients missing). The mean cyst size in these patients was 12 ± 6.30 mm in diameter with a volume of 509 ± 660 mm^3. One cyst had the same size as that before the

TABLE 4 Data at diagnosis, and at 1, 5 and 10 years after surgery (excluded were five patients operated later than the 1-year follow-up)

	Diagnosis n = 51 (42 f, 9 m)	1 Year n = 50/49[a]	5 Years n = 34/28[a]	10 Years n = 14/12[a]
Age (years)	49.5 ± 17.0 (19–78)			
Diameter (mm)	18.2 ± 6.19	4.6 ± 6.95	4.9 ± 5.75	8.1 ± 6.79
Volume (mm^3)	2473 ± 2972	197 ± 475	177 ± 308	485 ± 611
Any pituitary deficiency	33% (11 f, 6 m)	50% (20 f, 5 m)	62% (18 f, 3 m)	50% (6 f, 1 m)
GH-def	12% (3 f, 3 m)	16% (5 f, 3 m)	29% (8 f, 2 m)	29% (3 f, 1 m)
ACTH-def	25% (9 f, 4 m)	34% (12 f, 5 m)	32% (10 f, 1 m)	29% (3 f, 1 m)
TSH-def	25% (8 f, 5 m)	32% (11 f, 5 m)	47% (13 f, 3 m)	36% (4 f, 1 m)
LH/FSH-def	24% (7 f, 5 m)	24% (7 f, 5 m)	32% (8 f, 3 m)	29% (3 f, 1 m)
ADH-def	2.0% (1 f, 0 m)	14% (7 f, 0 m)	18% (6 f, 0 m)	7.1% (1 f, 0 m)
Visual field defects	47% (21 f, 3 m)[b]	26% (12 f, 1 m)	26% (8 f, 1 m)	7.1% (1 f, 0 m)[c]
Visual acuity imp	22% (10 f, 1 m)[b]	12% (6 f, 0 m)	12% (4 f, 0 m)	7.1% (1 f, 0 m)[c]

Note: Data are shown as mean ± SD. Range for age within parenthesis.

Cyst size (diameter and volume) was analysed with one-way ANOVA for data between 1, 5 and 10 years (diameter: F = 1.41, p = .25, volume: F = 2.23, p = .11)

Abbreviations: ACTH, adrenocorticotropic hormone; ADH, antidiuretic hormone; ANOVA, analysis of variance; f, female; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; m, male; MRI, magnetic resonance imaging; TSH, thyrotropin.

[a]One year: MRI data were not available for one patient. Five years: MRI data were not available for six patients. 10 years: MRI data were not available for two patients.

[b]At diagnosis data of visual impairment was not available for four patients.

[c]At 10 years data of visual impairment was not available for one patient.

surgery. Data for all patients at the 1-year follow-up were 4.6 mm in diameter and 197 mm^3 in volume (Table 4). Two patients were re-operated on at 2 and 3.5 years, respectively. Approximately half of the patients had a remnant or recurrence of the cyst at the fifth year of follow-up. No remnant of the cyst was observed in the two patients operated twice. The mean cyst size of all the patients at 5 years was 4.9 mm in diameter with a mean volume of 177 mm^3.

At diagnosis 12% had GH deficiency, approximately 25% had adrenocorticotropic hormone (ACTH), TSH and luteinizing hormone/follicle-stimulating hormone (LH/FSH) deficiency while 2% (one patient) had antidiuretic hormone (ADH) deficiency. After surgery, the number of patients with pituitary deficiencies increased to 16% for GH deficiency, to approximately 30% for ACTH and TSH deficiency and to 13% for ADH deficiency. The number of patients with LH/FSH deficiency was unchanged at 1 year but at 5 years approximately 30% had LH/FSH deficiency (Table 4).

In contrast, visual field defects decreased from 47% at diagnosis to 26% at the 1- and 5-year follow-ups. Similarly, visual acuity improved from 22% at diagnosis to 12% at follow-up (Table 4).

Twelve patients had follow-up data at 1, 5 and 10 years. After an initial decrease in mean cyst size from 20 mm in diameter at diagnosis to 6 mm 1 year after surgery, the cyst size increased to 7 mm at 5 years and 8 mm at the tenth year of follow-up (repeated measures ANOVA, $n = 11$ (one patient did not have data at 5 years) $F = 1.55$, $p = .23$, volume $F = 4.26$, $p = .029$). Seven patients had a remnant of the cyst at the first follow-up after surgery (one of them was one of the two reoperated patients) and after 10 years this number increased to eight. The number of patients with pituitary deficiencies increased after surgery, except for ADH deficiency, which remained unchanged. Visual fields and visual acuity normalized after surgery in all patients except one (data of visual fields/acuity at 10 years for one patient missing; for detailed information see Table S3).

Five patients with Rathke's cleft cysts underwent surgery after 1 year of follow-up. The duration to surgery varied between 3 and 9 years. One patient had both pituitary deficiency and visual impairment at diagnosis, but for unknown reasons, was not operated on until 4.5 years later. All but one of these patients did not have cyst remnants postsurgery (for detailed description see Table S4).

4 | DISCUSSION

To our knowledge, this is the largest study of both nonoperated and operated patients with Rathke's cleft cyst. Patients with Rathke's clefts cysts are a heterogenous group; therefore, we divided the patients into a group of patients with smaller cysts (<10 mm) and a group with larger cysts (≥10 mm). The size of the smaller cysts was stable over time, and pituitary deficiencies and visual impairment were rare. In addition, the majority of the larger cysts decreased over time, and only a few needed surgery. However, recurrence after surgery was frequent but only rare cases required a second operation. Visual field defects were common before surgery but improved postoperatively.

The natural history of Rathke's cleft cysts is multifaceted. A majority of published studies present predominantly operated patients and there are only a few studies with a long-term follow-up. There is a large variability in the results depending on the follow-up time and cyst size.[1,3,6,8-22] Unfortunately, also in the present study, very few cysts had a follow up of ≥10 years. One explanation could be that smaller cysts are usually not followed beyond 5 years. If they are unchanged in size and without any hormonal changes monitoring is considered complete. Another reason is that Rathke's cleft cysts were not registered in the first years of the Swedish Pituitary Registry and some regions still do not register small cysts routinely.

In the study by Aho et al.,[11] 61 patients with Rathke's cleft cyst were followed up for a period of 9 years. In 31% of these patients the cyst progressed over time, caused visual impairment and/or pituitary dysfunction and were therefore operated. For the remaining patients no cyst growth, visual disturbance or pituitary dysfunction were noted and surgery was therefore not indicated.[11] Culver et al.[17] studied 75 patients up to 10 years and found that 28% of the cysts increased in size whereas 57% were unchanged. In contrast, spontaneous involution of the cysts was reported in 31% of the patients in another study[23] whereas a Japanese study reported that the incidence of cyst growth was only around 5% during a mean period of 27 months.[24]

In the present study a small decrease in cyst size was observed over time in cysts with a diameter ≥10 mm that did not undergo surgery. It could be argued that this observation might be explained by the fact that cysts that increase in size are operated on and not included in this group. However, all operated cysts, except five, underwent surgery before the first-year follow-up and for the five patients who underwent surgery later, only one had a cyst that actually increased in size. It is worth mentioning that in one of these patients, the cyst disappeared temporarily and was not visible on MRI at the first year, but relapsed a few years later and was subsequently operated on.

The mechanism behind the regression of Rathke's cleft cysts over time has been suggested to be an absorption of cyst fluid, a rupture or several repeated ruptures over time.[25] Rathke's cleft cysts can also be complicated by bleeding and symptoms similar to pituitary apoplexy.[21] In our study, one patient with a cyst less than 10 mm and without visual disturbances was operated on. One reason to that could perhaps be bleeding in the cyst accompanied by acute headache. Symptoms like headache are also generally more common in patients with Rathke's cleft cysts but it might often improve irrespective of surgery.[22]

In the present study, the diagnosis of a Rathke's cleft cyst was based on the characteristic appearance on MRI. We cannot exclude the possibility that some of the cysts in the nonoperated group were cysts other than Rathke's cleft cysts. Although Rathke's cleft cysts are the most common cysts in this area other cysts such as arachnoid cysts, epidermoid cysts, craniopharyngeoma and cystic pituitary adenoma can also be seen. Even in operated patients the diagnosis could not always be confirmed because the histopathology reports were sometimes missing or usually were very sparse just containing protein and some epithelial cells.

A relationship between Rathke's cleft cysts and some types of craniopharyngiomas (papillary) has been suggested since they share some histopathologic features.[4] Approximately 20%—40% of the operated Rathke's cleft cysts have squamous metaplasia which may resemble the histopathology of papillary craniopharyngioma, making differential diagnosis difficult and may result in misclassification of some of the cysts.[6,26-28] The presence of squamous metaplasia has been associated with an increased risk of recurrence after surgery[6,11,12] and these metaplastic regions have been shown to have a higher Ki-67 proliferation index than the remainder of the cyst.[29] This also explains the various results of different studies. Recently, Brinkmeier et al.[30] showed that a specific transcription factor (Isl1) might be involved in the development of Rathke's cleft cysts, but not in craniopharyngioma.

In our review of the patients for this study, we found four craniopharyngioma, one nonfunctioning adenoma, three arachnoid cysts and one with an unclear diagnosis which were all excluded.

In addition to these patients with other diagnoses, we excluded some very small cysts (3 mm or less). The reason they were included in the Pituitary Registry is not known, as according to the Swedish National Treatment Guidelines cysts 3 mm or less in size are not in need of further follow-up. Nevertheless, an experienced neuroradiologist is important for the correct evaluation of MRI to avoid misdiagnosis and unnecessary follow-ups, and an increase in cyst size or MRI signal should lead to an increased attention. The most optimal care should then be decided at a multidisciplinary conference with the participation of a neurosurgeon, otologist, endocrinologist and neuroradiologist. This is the standard of care in Sweden and is used for all patients with pituitary–hypothalamic diseases.

Pituitary deficiencies and visual disturbances in patients with small cysts were rare but overall the most common pituitary deficiency in the total cohort of patients was gonadotrophin deficiency. Gonadotrophin deficiency was more often reported in males, but because of the binary registration in the registry, hormone levels were not available and further evaluation of other causes (weight changes, medication, etc.) was not possible. The second most common hormonal disturbance was a TSH deficiency, whereas diabetes insipidus was rare with a slight increase postsurgery. Worth to comment is also that the number of patients with GH deficiency might have been higher since we do not know how many of them were examined by a stimulation test of GH. However, overall, the results seem to be in line with those of earlier studies.[1,3,5-10,8-22]

Five years after surgery, half of our patients had a recurrence or relapse of the cyst. A residual cyst on postoperative MRI is associated with an increased risk of recurrence.[19] However, only two of our patients underwent surgery twice. As already discussed, the results from earlier studies vary significantly.[9,10,12-14,16-22] A large cohort of operated Rathke's cleft cysts was presented in a study by Aho et al.[11] They followed 160 patients with Rathke's cleft cysts for 5 years. A total of 118 were operated on and 97% of these patients had a complete resection with 18% developing recurrence at 5 years. As in our study, vision improved postoperatively and the number of patients with diabetes insipidus increased. In contrast, in the study by Aho et al.[11] pituitary deficiencies, except for ADH, improved in many of the patients. These results can be explained by many factors, such as the size of the cysts from the beginning, surgical factors and pathological factors. In the study from Aho et al.[11] recurrence was related to the use of fat and/or fascial graft at surgery closure and the presence of squamous metaplasia in the cyst wall. As discussed above, these cells have been shown to have an increased proliferation rate. In two other studies, the presence of squamous metaplasia, as well as the appearance on MRI, were related to recurrence.[6,12] In contrast, Billeci et al.[1] suggested that recurrence or relapse is probably more often due to incomplete surgical removal. Whether drainage of the cyst or cyst wall resection has the best result has also been discussed.[15,31,32]

In conclusion, patients with Rathke's cleft cysts are a heterogeneous group. In this study, we included smaller cysts that were not operated on. These cysts did not progress over time, and hormonal or visual disturbances were rare. We suggest that radiological follow-up of cysts less than 10 mm can be restricted to 5 years.

The majority of the larger cysts (≥10 mm) were also stable. Very few the cysts that were not operated on during the first year after diagnosis grew, and there was even a significant decrease in cyst size in the nonoperated cysts that were followed for 10 years. Despite postoperative recurrence or relapse in half of the patients, vision improved, while hormonal deficiencies remained stable over time. Only two patients required a second operation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Maria Petersson http://orcid.org/0000-0002-2970-8593
Bertil Ekman http://orcid.org/0000-0001-8732-7361
Per Dahlqvist http://orcid.org/0000-0002-6471-9503
Oskar Ragnarsson http://orcid.org/0000-0003-0204-9492

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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