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Clinical manifestations of Rathke's cleft cysts and their natural progression during 2 years in children and adolescents

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Ho-Seong Kim, MD, PhD Department of Pediatrics, Severance Children's Hospital, Endocrine Research Institute, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea Tel: +82-2-2228-2069 Fax: +82-2-393-9118 E-mail: kimho@yuhs.ac https://orcid.org/0000-0003-1135-099X Purpose: Rathke's cleft cyst (RCC) is an asymptomatic benign lesion. With increased interest in pediatric endocrinology, the prevalence of RCCs in children is also increasing. However, the clinical relevance and proper management of RCC is not well defined in children. Therefore, we investigated the clinical manifestations and radiologic features of RCC in children and adolescents, as well as the natural progression of RCC.

Methods: We retrospectively reviewed the medical records of 91 children and adolescents with RCC diagnosed with magnetic resonance imaging (MRI) in Severance Children's Hospital from January 2006 to December 2015. The clinical, hormonal, and imaging findings were analyzed in patient groups classified according to age. The size of each cyst was assessed in sixty patients who underwent follow-up MRI during the 2 years.

Results: Female patients were predominant (64 vs. 27). The common clinical features at presentation were endocrine dysfunction (59.3%), headache (23.0%), and dizziness (4.4%). Symptoms related to endocrine disorders were more frequent in younger patients. In 7 patients managed surgically, the cysts were significantly larger and more frequently located in the suprasellar region. Of 60 nonsurgical patients with a follow-up MRI performed within 2 years after the diagnosis, the RCC size increased in about 26.7% (n=16).

Conclusion: Although 94.4% of the patients with RCC had clinical symptoms, surgery was performed in only about 7.5% of patients. RCC is associated with pituitary insufficiency, thus, baseline and follow-up endocrine function tests are required. Additionally, regular MRI follow-up is required in long-term period to monitor change in size.

Keywords: Central nervous system cysts, Child, Adolescent, Endocrine system diseases, Hormones, Natural history

Introduction

Rathke's cleft cyst (RCC) is a benign, sellar, and/or suprasellar lesion originating from the remnants of Rathke's pouch, which disappears during the embryonic period^{1,2)}. RCCs are usually found incidentally in adults, with an incidence of about 12%–33% in autopsy cases³⁻⁶⁾. Although most cases of RCC are asymptomatic, some RCCs progress to enlarged cysts, leading to compression of adjacent structures and resulting in clinical symptoms such as headache, visual disturbance, and endocrinopathy. It is also assumed that the change of cyst in the size would be related to an imbalance between the secretion and absorption of cyst contents, and may cause leakage, intracystic hemorrhage, and infection^{7,8)}.

Recently, the prevalence of RCC in children is gradually increasing, owing to the increased

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number of work-ups for detecting growth and puberty disorders in children, as well as the improved quality of brain imaging, allowing the identification of RCC. However, most previous studies on RCC were based on adult data, and the number of enrolled patients was limited. In addition, the optimal guideline for the management of asymptomatic RCC is not well defined because of the uncertainty about the natural course of asymptomatic RCC.

In the present study, we aimed to investigate the clinical characteristics of RCC in children and adolescents, and the natural course of asymptomatic RCC in patients undergoing brain magnetic resonance imaging (MRI) at least 2 times during 2 years.

Materials and methods

1. Patients

Ninety-one patients with RCC (age, 1–18 years) who visited Severance Children's Hospital from January 2006 to December 2015 were included. RCC was diagnosed in these patients based on the results of sellar MRI. This study's protocol was approved by the Institutional Review Board of Yonsei University Severance Hospital (approval number: 4-2017-0121). Written informed consent was obtatined from all patients.

2. Analysis of clinical and radiological data

We obtained the baseline information of patients, including clinical symptoms, age, sex, height, weight, and body mass index, through a retrospective review of medical records. The patients were categorized according to age at diagnosis into the school-age group (subdivided into elementary and middle or high school) and the preschool-age group. The height standard deviation score (SDS) and weight SDS were adjusted for chronological age (CA) and sex were calculated by using the 2007 growth reference for Korean children and adolescents. Endocrinological evaluation included measurement of the bone age (BA) and the basal level of free thyroxine, thyroidstimulating hormone (TSH), insulin-like growth factor-I, insulin-like growth factor binding protein-3, luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol, testosterone, adrenocorticotropic hormone (ACTH), cortisol, and prolactin. Some selected cases required more detailed examinations, such as a combined pituitary function test or a gonadotropin releasing hormone (GnRH) stimulation test.

The following criteria were used for the diagnosis of various endocrine disorders. The definition of growth hormone deficiency (GHD) included (1) short stature, below the third percentile for age or >2 standard deviations below the mean stature; (2) a peak growth hormone (GH) level of <10 ng/ mL in 2 types of GH stimulation tests, by using levodopa and insulin; and (3) delayed BA comparing to CA. The criteria for the diagnosis of central precocious puberty (CPP) were (1) onset of pubertal characteristics before the age of 8 years in girls and 9 years in boys; (2) a peak LH level of >5 mIU/mL in the GnRH stimulation test; and (3) advanced BA comparing to CA. TSH deficiency was defined as the absence of a TSH increase during the thyrotropin releasing hormone stimulation test. ACTH deficiency was diagnosed when no increase in cortisol was elicited during the insulin tolerance test (peak cortisol level, <20 µg/dL). Lastly, hyperprolactinemia was defined as a baseline prolactin level of >25 ng/mL.

Diabetes insipidus (DI) was defined to the disease with polyuria and polydipsia which is originated from the deficiency of antidiuretic hormone.

The MRI findings of RCCs, confirmed by neurology radiologists, were classified based on different characteristics, such as the size (height and width), location, and signal intensities of T1- and T2-weighted images (high, equal, and low).

3. Statistical analysis

All statistical analyses were conducted with IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA). Continuous variables such as age, height, and weight are presented as the mean±standard. Categorical variables such as sex, clinical symptoms at diagnosis and MRI findings were expressed by using frequencies and percentages and were compared with

Table 1. Demographic and clinical characteristics of the 91	
patients included in the analysis	

Characteristic	Value
Age (yr), mean±SD (range)	9.7±4.2 (1.2-18.0)
Sex	
Male	27 (29.7)
Female	64 (70.3)
Height SDS	0.37±1.51
Weight SDS	0.30±1.27
Body mass index SDS	0.11±1.12
Endocrinologic abnormality , n (%)	54 (59.3)
Early puberty	34
Short stature	13
Polyuria	4
Galactorrhea	2
Menstrual problem	1
Neurologic abnormality , n (%)	32 (35.1)
Headache	21
Dizziness	4
Visual disturbance	3
Syncope	2
Seizure	1
Tinnitus	1
Asymptomatic, n (%)	5 (5.6)
Treatment	
Conservative management	84
Surgical management	7

SDS, standard deviation score.

other variables by using chi-square test. A *P*-value of <0.05 was considered significant.

Results

1. Baseline clinical characteristics of RCC

The demographic and clinical characteristics of 91 patients are shown in Table 1. Of total patients, 27 were boys (29.7%) and 64 were girls (70.3%). The mean age of the patients was 9.7 years (range, 1.2–18.0 years). More than half of the patients had symptoms related to the endocrine system (n=54, 59.3%), such as early puberty, short stature, polyuria, galactorrhea, and menstrual disturbance. Thirty-two patients (35.1%) had symptoms related to the neurologic system, such as headache (n=21, 23.1%), dizziness (n=4, 4.4%), and visual disturbance (n=3, 3.3%). In addition, asymptomatic patient was 5 (5.6%) (Table 1).

Fifty-one patients performed endocrinologic function test and Table 2 summarized the results. The most common endocrine dysfunction was CPP (n=36, 70.6%, 33 isolated, 3 combined endocrinopathy), followed by GHD (n=14, 27.5%, 5 isolated, 9 combined endocrinopathy), DI (n=3, 5.9%, 1 isolated,

Table 2. Results of endocrine evaluation in 51 patients

Variable	Total	Isolated	Combined
Central precocious puberty	36	33	3
Growth hormone deficiency	14	5	9
TSH deficiency	5	0	5
Diabetes insipidus	3	1	2
Hyperprolactinemia	2	1	1
ACTH deficiency	1	0	1
Gonadotropin deficiency	1	0	1
Normal	1	-	-

RCC, Rathke's cleft cyst; TSH, thyroid stimulating hormone; ACTH, adenocorticotropic hormone.

2 combined endocrinopathy), hyperprolactinemia (n=2, 3.9%, 1 isolated, 1 combined endocrinopathy), ACTH deficiency (n=1, 2.0%, 1 combined endocrinopathy) and gonadotropin deficiency (n=1, 2.0%, 1 combined endocrinopathy. Only 1 patient (2.0%) of them had normal results.

Ten of 91 patients (11.0%) were multiple endocrine dysfunction; three patients of GHD with CPP, 2 patients of GHD with DI, 2 patients of GHD with TSH deficiency, 1 patient of GHD, TSH deficiency with ACTH deficiency, 1 patient of TSH deficiency accompanying hyperprolactinmeia and 1 patient of GHD, TSH deficiency, and accompanying gonadotropin deficiency.

2. Clinical manifestations in the groups classified according to age

The presenting symptoms according to age group were analyzed (Table 3). In the preschool-age group (<7 years), early puberty (n=12, 46.2%), short stature (n=5, 19.2%), and headache (n=7, 27.0%) were common symptoms. Elementary-school children (7–12 years) also had symptoms of early puberty (n=22, 48.8%) and short stature (n=5, 11.0%), but presented with a greater variety of neurological symptoms than the other groups. Lastly, the middle school or high school group (>12 years) mainly experienced neurological symptoms, such as headache (n=9, 45.0%). Clinical symptoms related to endocrine system, especially related to growth and puberty appeared significantly more frequent in before-middle school patients than in middle or high school aged patients (P<0.01).

3. Clinical characteristics of the patients who underwent surgery

Seven patients underwent surgical treatment, either in an attempt to resolve pressure symptoms such as headache and visual field defect or to investigate the possibility of malignancy (Table 4). In all 7 patients who underwent surgery, the selected

Table 3. The incidence of chief complaints in patients with RCC, stratified to age group

Variable	Preschool (<7 yr, n=26)	Elemantary school (7–12 yr, n=45)	Middle or high school (>12 yr, n=20)	P-value
Endocrine (n=54, 59.3%)				<0.01
Short stature	5 (19.2)	5 (11.0)	3 (15.0)	
Early puberty	12 (46.2)	22 (48.8)	0 (0)	
Dysmenorrhea	0 (0)	0 (0)	1 (5.0)	
Polyuria	0 (0)	3 (6.7)	1 (5.0)	
Galactorrhea	0 (0)	0 (0)	2 (10.0)	
Neurologic (n=32, 35.1%)				0.130
Headache	7 (27.0)	5 (11.0)	9 (45.0)	
Dizziness	0 (0)	3 (6.7)	1 (5.0)	
Syncope	0 (0)	1 (2.2)	1 (5.0)	
Seizure	1 (3.8)	0 (0)	0 (0)	
Tinnitus	0 (0)	1 (2.2)	0 (0)	
Visual disturbance	0 (0)	2 (4.5)	1 (5.0)	
Asymptomatic (n=5, 5.5%)	1 (3.8)	3 (6.7)	1 (5.0)	0.33

Values are presented as number (%).

RCC, Rathke's cleft cyst.

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operation method was transsphenoidal aspiration and the RCC was confirmed pathologically. After the operation, clinical symptoms related to pressure were improved after surgery in all 7 patients. On the other hand, the endocrine functions were aggravated in 2 of 7 patients, improved in 1 patient, and remained the same in 4 patients after surgery (Table 4). None of the 7 patients experienced recurrence of RCC.

We also analyzed the characteristics of RCC comparing 2 groups, surgical treatment group and nonsurgical treatment group. The RCC size of patients who required surgery was significantly larger than that of patients who did not underwent surgery (Table 5). Moreover, the RCC was more frequently located in suprasellar in patients who required surgical treatment. However, there were no differences signal intensities between surgical and nonsurgical group.

Natural progression of RCC size on image study of during 2 years

Sixty patients among total 31 patients underwent followup MRIs during 2 years. Follow-up MRIs showed that the size of RCCs increased in 16 of 60 patients (26.7%), remained the same in 21 patients (48.3%), and decreased in 15 of 60 patients (25.0%). None of the patients with increased size of RCCs needed the surgical treatment in follow-up period.

Discussion

We evaluated the clinical characteristics of 91 children and adolescents with RCCs diagnosed with sellar MRI, and analyzed the presenting symptoms in the groups classified according to age. Our study demonstrated a female preponderance in RCC, as in previous studies of adults^{9,10)}. Presenting symptoms related to CPP, which is more common in girls than in boys, and menstrual disorders which are also presented only in girls may lead to frequent detection of RCC in female. On the other hand, the most 2 common chief complaints of boys were short stature (37.0%) and headache (25.9%), differently from those of girls early puberty (48.4%) and headache (23.4%).

In this study, symptomatic RCC was noted in most of the patients (86 of 91 patients, 94.4%), whereas asymptomatic RCC was observed in only 5.6% (5 of 91 patients). The frequency of each symptom in symptomatic RCC patients has been reported to be variable owing to the diversity of the enrolled patient cohorts^{8,9,11-13)}. Previous studies of adults' data reported that frequent clinical symptoms of RCC include headache, visual disturbance, and pituitary dysfunction. The prevalence of each clinical symptom showed wide ranges according to studies. Headache appeared in 44%-81% of patients, visual disturbance in 11%-67%, and pituitary dysfunction in 30%-60% of symptomatic cases^{9,10)}. In the present study, headache (n=21, 23.1%) and visual disturbance (n=3, 3.3%) were less frequently observed, and pituitary dysfunction (n=54, 59.3%) showed a similar incidence to that reported in previous studies. Especially, pituitary dysfunction related to growth or puberty, such as short stature and early puberty appeared to only children or adolescents of our study differed from previous studies. Furthermore, analysis of the presenting neurologic symptoms in the groups classified according to the age showed that headache

Table 5. Comparison of magnetic resonance imaging findings between the surgical and medical management groups

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Variable	Medical (n=84)	Surgical (n=7)	P-value
Size, height (mm)	6.4±3.5	14.0±7.2	0.05
Size, width (mm)	10.1±3.7	15.0±4.1	< 0.01
Location			< 0.01
Suprasella	8 (9.5)	3 (42.8)	
Pars intermedia + supra extension	3 (3.6)	2 (28.6)	
Pars intermedia	73 (86.9)	2 (28.6)	
T1 intensity			0.07
Hypointense	23 (27.4)	0 (0)	
lsointense	13 (15.5)	4 (57.1)	
Hyperintense	48 (57.1)	3 (42.9)	
T2 intensity			0.16
Hypointense	68 (81.0)	4 (57.1)	
lsointense	8 (4.5)	2 (28.6)	
Hyperintense	8 (4.5)	1 (14.3)	

Values are presented as mean±standard deviation or number (%).

Table 4. Characteristics of seven patients who underwent surgery

Patient No.	Age (yr)/sex	Reason for surgery	Outcome	Cyst size (height×width, mm)	Preop endocrine disorder	Postop endocrine disorder	Recurrence
1	9/F	Headache	Improved	14.2×19.1	GHD	Multiple [*]	No
2	15/M	Headache	Improved	13.3×9.4	GHD	Multiple [†]	No
3	10/M	Visual field defect	Improved	28×18.1	Multiple [‡]	Multiple [‡]	No
4	10/F	Suspected malignancy	None	11.7×17.1	Normal	Normal	No
5	15/F	Suspected malignancy, headache	Improved	8.2×11.1	GHD	Normal	No
6	18/M	Suspected malignancy, headache	Improved	8.6×15.7	Multiple [†]	Multiple [†]	No
7	12/F	Visual field defect	Improved	18.2×20.1	Multiple [‡]	Multiple [‡]	No
D				1.6.1			

Preop, preoperative; postop, postoperative; GHD, growth hormone deficiency.

*GHD, thyroid stimulating hormone deficiency, and gonadotropin deficiency. [†]GHD, adrenocorticotropic hormone deficiency, and thyroid stimulating hormone deficiency. [‡]GHD and diabetes insipidus.

and visual disturbance were more common in older children and adolescents, however it does not have significant difference.

Further hormonal study revealed that most of the patients (98.0%) had pituitary dysfunction, which manifested as CPP, GH deficiency, multiple pituitary hormone deficiency, hyperprolactinemia, and DI. According to the previous several studies of adults, prevalence of pituitary dysfunction in adults ranged from $30.0\%-100.0\%^{14}$.

In previous studies, the indications for the surgical treatment of patients with RCC were controversial. Although the conventional therapy for symptomatic RCCs is surgical resection, not all cases of symptomatic RCCs require surgery for resection-only RCCs with pressure symptoms require surgery. Conservative care with follow-up MRI is recommended in cases of silent RCCs or smaller cysts with mild symptoms, and surgery is preferable for larger cysts with definite pressure symptoms¹⁵. In our study, 7 patients were operated by transsphenoidal microscopic surgery either to alleviate pressure symptoms or to investigate the possibility of malignancy because of the increasing size of the RCC. RCC was confirmed pathologically in each of these cases. All 7 patients experienced improvement of clinical symptoms after surgery; however, their endocrine dysfunctions did not improve, or was even aggravated in 2 patients. This is one of the reasons for the controversy about the operative treatment of RCC. Because radical resection may lead to a lower recurrence and a higher risk of additional endocrine disorders, transsphenoidal microscopic surgery is the first choice for surgical treatment^{12,16,17)}. In addition, follow-up endocrine surveillance is needed after surgical interventions. The several MRI features differed significantly between patients who underwent surgery and those who did not. RCCs were significantly larger and were more frequently located in the suprasellar region in patients who underwent surgery. Otherwise, we could not find any difference of intensity in the T1- or T2-weighted MRI images between patients who underwent surgery and those who did not. RCCs usually appear as homogenous intensity in the region of the pars intermedia⁷. The homogeneous signal observed in MRI can vary depending on the concentration and composition of the cyst contents, particularly protein, cholesterol, and hemorrhage18-20). Cysts with high protein contents display high intensity in T1-weighted images, and cysts with low water content show low intensity in T2-weighted images^{21,22)}. Lesions with high or low intensity in T1-weighted images and low intensity in T2-weighted images were most common in our study and consistent with findings reported in the literature^{22,23)}.

Lastly, follow-up MRI was performed in sixty of the 91 patients during 2 years, which showed that the size of RCC increased in 16 of 60 patients (26.7%), remained the same in 29 of 60 patients (48.3%), and decreased in 15 of 60 patients (25.0%). Our study demonstrated that most cases of RCCs without pressure symptoms remain the same or decrease in size over time. Further studies about the effect of medical treatment on RCC are required.

Considering limitations of our study, according to age and

In conclusion, it is necessary to perform both baseline and routine follow-up endocrine testing to detect endocrine dysfunction, because many patients with RCC may have symptoms related to pituitary dysfunction. Surgical resection is required only in RCC cases with pressure symptoms and conservative management of patients with RCC is recommended, in the absence of pressure symptoms. In addition, followup MRI is required, because the size of RCC can change after few years.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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