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ORIGINAL ARTICLE

Magnetic resonance imaging, clinical manifestations, and management of Rathke's cleft cyst

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Summary

Objective The management of Rathke's cleft cyst (RCC), particularly in patients with no symptoms or with only minor endocrinopathies, has not yet been established. We retrospectively analysed patients with RCC to elucidate correlations between the clinical manifestations, magnetic resonance imaging (MRI) findings, histology and therapeutic outcomes.

Methods We retrospectively studied 37 patients with RCC, who underwent computed tomography (CT), MRI and endocrinological examinations, of whom 27 patients underwent surgical intervention.

Results The presence of frontal headaches and anterior pituitary dysfunction was unrelated to the cyst size but was more frequent in patients with high- and isointensity cysts on T1-weighted images (WIs) than those with low-intensity cysts ($P = 0{\cdot}0159$ and $P = 0{\cdot}0249$, respectively). All three patients with posterior pituitary dysfunction had a high-intensity cyst on T1-WI ($P = 0{\cdot}0385$), whereas pituitary dysfunction was not observed in patients with a low-intensity cyst on T1-WI. In contrast to the excellent therapeutic outcomes with regard to visual disturbance and hyperprolactinaemia, recovery of pituitary dysfunction was rare; only three of nine patients with hypopituitarism showed improvement. Among six patients with histologically recognized intense chronic inflammation in the cyst wall, five patients had an RCC of T1 high intensity ($P = 0{\cdot}0161$), two patients had distinct rim enhancement on MRI ($P = 0{\cdot}0060$), all patients had frontal headaches ($P = 0{\cdot}0130$), and four patients had associated hypopituitarism ($P = 0{\cdot}0243$), none of which improved after surgical intervention.

Conclusion RCCs of high- and isointensity on T1-weighted images, which contain mucous material within the cyst, may be associated with chronic inflammation that can potentially cause irreversible endocrine dysfunction. In asymptomatic patients with RCCs of these MR intensities, close follow-up with precise endocrinological evaluation and gadolinium-enhanced MRI is necessary to avoid occult progression of the inflammation.

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Introduction

Rathke's cleft cyst (RCC) is an epithelial cell-lined cystic lesion of the pituitary that is believed to derive from remnants of Rathke's pouch, a dorsal invagination of the stomodeal ectoderm. Although they are common findings at autopsy, most remain asymptomatic throughout an individual's lifetime. When they do become symptomatic, however, their clinical manifestations are somewhat different from those of the most common pituitary tumour, adenoma. RCCs usually present with headaches, hypopituitarism of varying degrees and visual disturbance, followed by diabetes insipidus.[1–4] A few RCCs may show spontaneous resolution,[5] but little is known about the natural history of this benign lesion. As a result of modern neuroimaging techniques, and magnetic resonance imaging (MRI) in particular, RCCs are now being found with increasing frequency. However, at present the management of patients with RCC found incidentally, or presenting with minor symptoms, has not been established. In this retrospective study, we analysed patients with RCC to identify possible correlations between the clinical manifestations, MRI and histological findings. The purpose of this study was to (1) elucidate underlying mechanisms of the clinical manifestations in RCC, and (2) to establish a therapeutic strategy.

Patients and methods

We retrospectively studied 27 patients with histologically proven RCC and 10 patients with a radiological diagnosis of RCC. No patient had received any treatment previously. The 37 patients consisted of eight men and 29 women, with the age at diagnosis ranging from 19 to 78 (mean 45) years. All patients underwent radiological studies, including craniogram, computed tomography (CT) and MRI, as well as endocrinological and visual examinations. The follow-up period averaged 43 months, ranging from 4 to 105 months.

The size and location of the cysts were estimated by MR images with and without Gd-enhancement of axial, sagittal and coronal sections. CT density and signal intensities on T1- and T2-weighted images (WIs) of the cystic content were evaluated (Fig. 1a–c). In

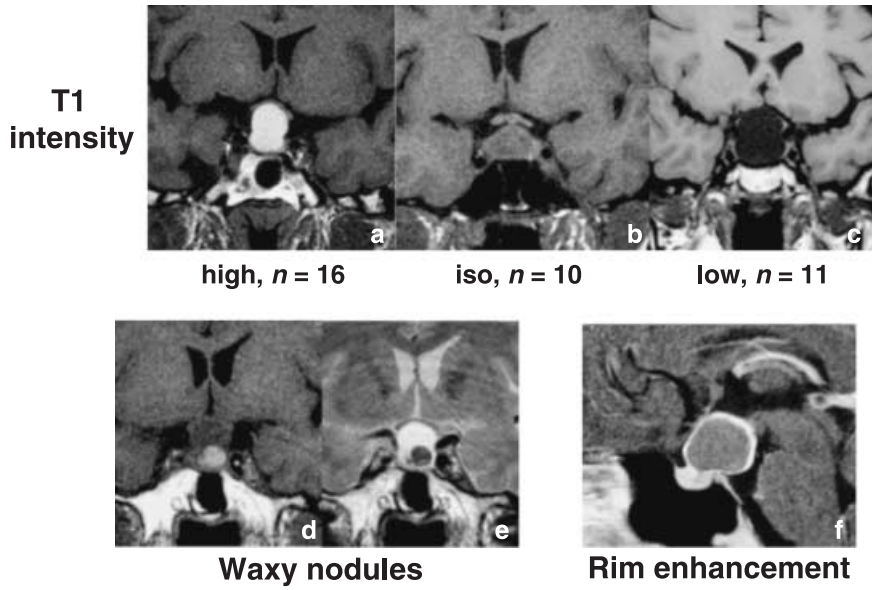

Fig. 1 T1-weighted coronal (a–e) and Gd-contrast-enhanced sagittal (f) MRI of Rathke's cleft cysts. Although MR intensity of the cysts is variable, it is homogeneous beside a waxy nodule, demonstrated as a T1-high (d) and T2-low (e) signal intensity mass within the cyst. (f) Entirely suprasellar Rathke's cleft cyst showing distinct rim enhancement.

addition, the presence of a waxy nodule, usually observed as a non-enhanced T1-high and T2-low signal intensity mass within the cyst (Fig. 1d,e), was examined.

Endocrinological evaluation included measurement of baseline levels of ACTH, cortisol, TSH, free T3, free T4, GH, PRL, LH, FSH, and testosterone or oestradiol. Dynamic stimulation tests either with regular insulin (0·1 U/kg), TRH (500 μg) and GnRH (100 μg) or with CRH (100 μg), GHRH (100 μg), TRH (500 μg) and GnRH (100 μg) were performed in every patient. No patient had primary disturbance(s) in thyroid, adrenal and/or gonadal functions. The criteria for diagnosing hypopituitarism were as follows: (1) hypocortisolism in patients with a low cortisol level and decreased or no ACTH response to the stimulation test; (2) hypothyroidism in patients with a low free T4 level and decreased or no TSH response to the stimulation test; (3) hypogonadism in women with a low basal level and decreased or no response to the stimulation test of LH and/or FSH; and (4) hypogonadism in men with a low testosterone level and decreased or no LH and/or FSH responses to the stimulation test. Diagnosis of panhypopituitarism was made when these three axes were all disturbed. One patient had an associated ACTH-producing microadenoma. Hyperprolactinaemia due to pharmacological and other medical causes was excluded. Diagnosis of diabetes insipidus was obtained by the water dehydration test and the pitressin test.

Among 27 histologically verified cases, 26 underwent transsphenoidal surgery (TSS) and one patient, who had an entirely suprasellar RCC, underwent transcranial surgery. The reasons for surgical intervention were as follows: visual disturbance in 13 patients, hypopituitarism in six patients, associated ACTH-producing microadenoma in one patient, severe headaches in four patients, and their choice to undergo surgery in three patients. It had been our policy to partially remove the cyst wall and to perform reconstruction of the sellar floor when intraoperative cerebrospinal fluid (CSF) leakage was encountered.

However, the 10 patients who did not undergo surgical intervention had a pure single cystic sellar lesion. Surgery was not performed in one patient with visual disturbance and in another with hypopituitarism because the cyst resolved spontaneously. One elderly patient with syndrome of inappropriate secretion of ADH (SIADH) refused surgery. The other seven patients were either asymptomatic or presented only with headaches. None of them had accompanying calcification or showed enlargement or destruction of the sella turcica. During the follow-up, all cysts remained unchanged both in size and intensity, apart from the two cysts that resolved spontaneously. Four cysts had waxy nodules, eight cysts had high- or isointense content on T1-WI, and no cyst was both low in CT density and T1 intensity. The MR signal intensity of the cysts, excluding the waxy nodules, was homogeneous in all 10 cases. There was no difference in terms of age, gender, symptoms, cyst size, and findings of CT and MRI between patients with and without surgical intervention.

The Mann–Whitney *U*-test and χ^2-analyses were used for statistical analysis.

Results

Neuroimaging features

On CT, the cystic content was high density in 20 patients, isodense in seven, and low density in 10. Signal intensities on T1- and T2-WIs of the cyst were as follows: high intensity in 16 and 28 patients, isointense in 10 and six patients, and low intensity in 11 and three patients (Fig. 1a–c), respectively. Waxy nodules were found in 16 patients (43·2%). The maximum diameter of the cyst ranged from 10 to 38 (17·9 ± 7·6) mm. The Gd-enhanced study was useful in detecting the pituitary gland; it was displaced anteriorly in 24 patients, inferiorly in eight patients, superiorly in one patient and laterally in another, and was unclear in three patients. Two patients had an entirely suprasellar RCC. However, determining the presence of enhancement of the cyst wall was difficult in many cases. Although distinct rim enhancement was negative in most patients, it was observed in three patients (Fig. 1f). There was a correlation between low-density cysts on CT and high-intensity cysts on T2-WI ($P = 0{\cdot}0358$). There was no other correlation among age, gender, cyst size, location, CT and MRI findings.

Table 1. Correlations between clinical symptoms and cyst intensity on the T1-weighted image

Clinical symptoms	T1 intensity			
	High ($n = 16$)	Iso ($n = 10$)	Low ($n = 11$)	*P*-value (χ^2)
Headaches ($n = 18$)	8	8	2	0·0159*
Visual disturbance ($n = 14$)	5	4	5	(–)
Adenohypophysial dysfunction ($n = 9$)	6	3	0	0·0249*
Hyperprolactinaemia ($n = 7$)	0	2	5	0·0073*
Neurohypophysial dysfunction ($n = 3$)	3	0	0	0·0385†
Spontaneous resolution ($n = 3$)	1	2	0	(–)

*Statistical significance between high + iso and low;
†Statistical significance between high and iso + low.

Correlations between symptoms and imaging (Table 1)

Frontal headache was the most common symptom, occurring in 18 patients (48·6%), and was the only presentation in seven patients. Seven patients suffered sudden and severe headache mimicking that of pituitary apoplexy and five of them had repeated episodic headaches. In addition to frontal headaches, many patients complained of deep orbital pain.[6] The presence of headaches did not correlate with cyst size but was more frequent in patients with high- and isointensity cysts than those with low-intensity cysts on T1-WI ($P = 0·0159$).

Visual disturbances, including disturbance of visual acuity and visual field defects, were observed in 14 patients (37·8%). The size of RCC correlated with the presence of visual disturbance ($P < 0·0001$). Optic nerve or chiasm was markedly compressed by RCC in these patients. No other CT or MRI findings showed any correlation.

Anterior pituitary dysfunction was observed in nine patients (24·3%) (Table 2). Three patients had panhypopituitarism and six patients had partial hypopituitarism: hypogonadism in four women (two pre- and two postmenopausal), hypocortisolism in three women, and hypothyroidism in one woman. Besides two young women with hypogonadism who presented with dysmenorrhoea, four women with partial hypopituitarism were either asymptomatic or complained of very minor fatigue and cold intolerance. None of the nine patients had hyperprolactinaemia. Hypopituitarism did not show any correlation with cyst size: the size of the nine cysts ranged from 10 to 38 (19·8) mm. Meanwhile, hypopituitarism was observed only in patients with high- or isointensity cysts but not in patients with low-intensity cysts on T1-WI ($P = 0·0249$). All three patients with panhypopituitarism had a high-intensity cyst on T1-WI. No other findings on CT and MRI correlated with the presence of hypopituitarism.

Seven patients (18·9%), none of whom had hypopituitarism, were found to have elevated prolactin levels of 30–100 μg/l. Hyperprolactinaemia was more common in patients with low-intensity cysts on T1-WI ($P = 0·0073$) or cysts without waxy nodules ($P = 0·0103$). Age, gender, size and other imaging findings did not correlate with the presence of hyperprolactinaemia.

Disturbance of posterior pituitary function was observed in three patients (8·1%): two patients with diabetes insipidus and one with SIADH. Their RCCs were high intensity on T1-WI ($P = 0·0385$), but showed no other correlation with cyst size or other imaging findings.

Spontaneous resolution of the cyst occurred in three patients (8·1%). One patient underwent TSS and two patients did not. No difference was found in symptoms, size and imaging findings between cases of RCC with and without spontaneous resolution. On the contrary, one patient developed panhypopituitarism with enlargement of RCC 3 years after the initial manifestation of episodic headache.

Therapeutic outcomes

Among 15 patients who underwent TSS, frontal headaches improved in 12 patients (80·0%). Episodic headaches disappeared in all patients. Visual disturbances improved in all 13 patients immediately after TSS and transcranial surgery, and in one patient after spontaneous resolution of the cyst. Elevated prolactin levels also reduced to the normal range in all four patients after TSS and in one patient after a spontaneous resolution. By contrast, improvement in hypopituitarism after TSS was noted in only three patients (37·5%) who had partial insufficiency: two women with hypogonadism and one patient with hypocortisolism. In two young women, dysmenorrhoea

Table 2. Summary of six patients with hypopituitarism

Case no.	Age/Sex	Hypopituitarism	Size (mm)	T1-signal intensity	Waxy nodules	Inflammation on cyst wall	Endocrinology results
1	49/F	C + T + G	38	High	(+)	(+)	NC
2	45/M	C + T + G	26	High	(–)	(+)	NC
3	40/F	C + T + G	25	High	(–)	(+)	NC
4	69/F	C + G	14	High	(+)	(–)	C: improved
5	76/F	C + G	10	High	(+)	(+)	NC
6	68/F	C	20	Iso	(+)	(–)	NC
7	37/F	T	16	High	(–)	NE	NC
8	23/F	G	15	Iso	(–)	(–)	G: improved
9	26/F	G	14	Iso	(+)	(–)	G: improved

M, male; F, female; C, hypocortisolism; T, hypothyroidism; G, hypogonadism; NE, not examined (because cyst resolved spontaneously); NC, no change.

Table 3. Correlations between cystic contents and cyst intensity on T1-weighted image

Cystic contents	T1 intensity		
	High ($n = 11$)	Iso ($n = 7$)	Low ($n = 9$)
Cerebrospinal fluid-like ($n = 2$)	0	0	2
Xanthochromic ($n = 5$)	0	0	5
Mucous material with low viscosity ($n = 11$)	4	5	2
Mucous material with high viscosity ($n = 9$)	7	2	0

Statistical significance between high + iso and low: $P < 0{\cdot}0001$.

improved, with normal LH and FSH responses to the stimulation test. Both cortisol level and ACTH response to the stimulation test improved to normal in one patient. No other improvement, including three patients with panhypopituitarism, was observed (Table 2). Diabetes insipidus also persisted in one patient each, after TSS and spontaneous resolution of the cyst.

Postoperative CSF rhinorrhoea occurred in two patients who were treated by spinal CSF drainage. Four patients had transient postoperative diabetes insipidus. One patient had developed transient hemiparesis a few days after TSS due to cerebral vasospasm. There was no mortality and no permanent morbidity in 27 patients who underwent surgical intervention. Among 29 patients who underwent surgery and whose cyst showed spontaneous resolution, asymptomatic recurrence of RCC was noted on MRI in seven patients.

Correlations between pathological features and imaging

Macroscopic findings of the cystic content in 27 surgical cases were as follows: CSF-like fluid in two cases, xanthochromic fluid in five, mucous material with low viscosity in 11, and mucous material with high viscosity in nine. All 18 RCCs of high- and isointensity on T1-WI contained mucous material of various degrees, whereas only two RCCs of T1 low intensity contained mucous material with low viscosity ($P < 0{\cdot}0001$, Table 3). In all 13 patients with waxy nodules on MRI, yellow waxy masses were observed. One RCC contained blood clots.[6]

Histological examination in 27 patients demonstrated an epithelial lining with various features. Pseudostratified columnar and simple cuboidal or columnar epithelium with or without cilia was the most common feature, whereas squamous metaplasia was observed in three patients. Various changes indicating intense chronic inflammation, particularly thick granulation tissue, was recognized in six patients. Apart from one patient who presented with symptomatic haemorrhage within the cyst,[6] five patients had an RCC of high intensity on T1-WI ($P = 0{\cdot}0161$). Two patients had distinct rim enhancement on MRI ($P = 0{\cdot}0060$). All six patients had headaches ($P = 0{\cdot}0130$) and four patients presented with anterior pituitary dysfunction ($P = 0{\cdot}0243$): one with partial and three with total hypopituitarism, none of which showed improvement of pituitary dysfunction following TSS. Co-inversely, all three patients with panhypopituitarism in the present series had an RCC of T1 high intensity, contained mucous material with high viscosity, demonstrated intense inflammation on histology, and showed no improvement in pituitary dysfunction after TSS.

Discussion

The MR appearance of RCC is highly variable and neuroimaging diagnosis of RCC is often difficult. However, a few key findings that may help to distinguish RCC from other cystic lesions have been reported. RCCs usually do not exhibit destruction or enlargement of the sella turcica.[7] Intracystic nodules, that is waxy nodules, if present, show characteristic intensity on MRI.[8] RCCs are almost always homogeneous in MR intensity, except for waxy nodules, whereas other lesions such as cystic craniopharyngioma and haemorrhagic adenomas are less frequently homogeneous.[9] These findings were confirmed in the present study. We suggest that the presence of waxy nodules, although not found in every case, is the most reliable diagnostic indicator of RCCs. CT density and MR intensities of RCCs vary considerably depending on the cystic content. A high T1-WI intensity has been interpreted to indicate a high content of protein and mucopolysaccharide[10,11] and, rarely, haemorrhage.[6] The cystic content of high- and isointensity RCCs on T1-WI is usually mucus with varying viscosity.[4,5,11] By contrast, RCCs with low intensity on T1-WI usually contain CSF-like transparent fluid with low viscosity.

The clinical manifestations of RCCs are also varied and are slightly different from those of adenomas. RCCs are occasionally accompanied by chronic inflammation around the cyst wall.[1,2,4,6,11–15] The inflammation is basically a foreign-body reaction to the cystic content, mucus, and may extend to surrounding tissue.[12,13,15] Mucus is a strong stimulator of tissue inflammatory response. It has been suggested that such inflammation, rather than simple compression by the cyst, participates in the development of characteristic symptoms.[1,2,12–14] In the present study, the content of RCCs with intense chronic inflammation showed high intensity on T1-WI and consisted of viscous mucous material. Most of the patients presented with pituitary dysfunction. Frontal headaches and anterior or posterior pituitary insufficiency were more frequently seen in patients with high- or isointense RCC contents than those with low-intensity contents on T1-WI. Cyst size did not correlate with the presence of pituitary dysfunction. This is different from the situation with adenomas, which usually develop hypopituitarism only when they become large tumours. Thus we considered that chronic inflammation had participated in the development of pituitary dysfunction in many cases, and not only in cases confirmed by histology. Saeki *et al.*[5] also reported that RCCs with iso- to high-intensity on T1-WI cause clinical symptoms with a smaller size than cysts of low intensity.

Therapeutic results of hypopituitarism and diabetes insipidus in patients with RCC have been reported to be disappointing,[1–4] including the present series. The poor endocrine prognosis has also been suggested to be due to inflammation of the adenohypophysis or neurohypophysis.[4,13] In the present study, hypopituitarism showed no improvement after surgery in patients with histologically proven intense chronic inflammation. The inflammation may extend to and destroy the pituitary gland, thus resulting in irreversible endocrine dysfunction.

Visual disturbances and hyperprolactinaemia are also common manifestations in RCCs as in large adenomas. In the present study, the presence of visual disturbances was associated with large RCC but showed no correlation with MR intensity. Hyperprolactinaemia was frequent in patients with low-intensity cysts on T1-WI. Their therapeutic results were excellent: visual disturbances and hyperprolactinaemia improved in every patient with surgery or with spontaneous resolution of the cyst. We suggest that simple compression of the chiasm or the stalk by the cyst may have been the major causative factor of these symptoms.

At present, surgery is definitely indicated in RCC cases with evident clinical symptoms, particularly visual disturbances. However, we must try to identify chronic inflammation as soon as possible in such cases to avoid irreversible endocrine dysfunction.[13] Inflammation will not improve as long as the causative factors, that is the contents of the cyst, remain in the pituitary.[13] Rim enhancement of the cyst seen on MRI may indicate chronic inflammation of the cyst wall,[4] although such correlation was confirmed in only two patients in this study. Accordingly, pituitary function must be evaluated precisely to detect even minor endocrinopathies in asymptomatic patients. In contrast to panhypopituitarism, partial hypopituitarism, and particularly hypogonadism in young women, may have a higher chance of improving after adequate surgery. Thus TSS should be considered in patients suspicious of RCC with mild pituitary insufficiency to prevent further development of hypopituitarism.[2] Although headaches might have been unrelated to RCC in some patients, 80% of them improved after treatment. Frontal headaches, particularly episodic headaches, may also indicate intermittent inflammatory reactions.[14] One patient in our series developed panhypopituitarism 3 years after the initial manifestation of episodic headache. Thus, patients with episodic headaches may also be considered as candidates for TSS to prevent the extension of inflammation. However, asymptomatic patients with normal pituitary function, usually incidental cases, should be treated conservatively.[2,5] Close follow-up with endocrinological evaluation and Gd-enhanced MRI is necessary in patients with T1 high- and isointensity cysts. When minor decline of pituitary function or rim enhancement is recognized during follow-up, surgical treatment should be considered.

Apart from entirely suprasellar RCC that usually requires transcranial surgery,[16] most patients can be treated successfully with TSS. Decompression by partial removal of the cyst wall achieved satisfactory results in the present series. Although total resection of RCC may further decrease the risk of recurrence,[4,14] partial removal may be indicated in most patients as an initial procedure.[1–3,9]

Conclusion

In conclusion, at present, surgical indication of RCC may include those with visual disturbance, endocrinopathies and, possibly, episodic severe headaches. Many characteristics of RCCs, including clinical manifestations and MRI findings, are caused by mucous material within the cyst and the subsequent inflammatory reaction. It should be kept in mind in managing patients with RCC, particularly in those with high- and isointensity on T1-WI, that not only the size of the cyst but also the surrounding inflammation contributes to the development of the clinical features.

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