

Panhypopituitarism due to Pituitary Cyst of Rathke's Cleft Origin —Two Case Reports

J J Mukherjee,*^{FAMS, MBBS, MRCP (UK)}, C H Lee,**^{FAMS, MBBS, MRCP (UK)}, P L Ong,***^{FAMS, PPA, FRACS (Neurosurg)},
J Teo,****^{FAMS, FRCPA, MIAC}

Abstract

Introduction: Rathke's cleft cysts are cystic sellar and suprasellar lesions, characteristically lined by a single layer of ciliated cuboidal or columnar epithelium. **Clinical Picture:** We report 2 patients who presented with gastrointestinal symptoms and were initially investigated for dyspepsia. However, attention was subsequently drawn to persistent hyponatraemia that led to the diagnosis of panhypopituitarism due to Rathke's cleft cyst. **Treatment:** Transsphenoidal surgery followed by drainage of the cyst and partial excision of the cyst wall in both patients. **Outcome:** No recurrence of the lesions over a mean follow-up of 16 months. There has been an improvement of the hypothalamo-pituitary-adrenal axis in 1 patient and the hypothalamo-pituitary-thyroid axis and visual fields in the other. **Conclusion:** Symptomatic Rathke's cleft cysts are rare and can occasionally cause panhypopituitarism. Ideal management of these cysts is unclear, but aspiration followed by partial excision of the cyst wall seems the best initial option.

Ann Acad Med Singapore 2001; 30:651-5

Key words: Cysts, Pituitary tumours, Rathke's cleft cyst

Introduction

Rathke's cleft cysts are non-neoplastic cystic epithelial lesions of the sellar and suprasellar region which are thought to originate from the remnants of Rathke's pouch and are characteristically lined by a single layer of ciliated cuboidal or columnar epithelium with goblet cells.^{1,2} However, foci of squamous epithelium in Rathke's cleft cysts have also been reported.³⁻⁵

Small asymptomatic Rathke's cleft cysts are not uncommon and have been reported at autopsy in 13% to 22% of normal pituitary glands.^{6,7} However, symptomatic Rathke's cleft cysts are rare and only approximately 150 cases had been reported till 1991.⁸ The increasing use of magnetic resonance imaging (MRI) has resulted in more Rathke's cleft cysts being detected over the past decade.⁹⁻¹¹ The usual management of these cysts has been simple surgical drainage with partial excision of the cyst wall.¹² Routine postoperative radiotherapy has not been advocated, as recurrence is rare and limited to isolated case reports.^{9,10,12-15}

We report our experience with the management of 2 patients with symptomatic Rathke's cleft cyst and review the literature with respect to their presentation, radiological features and recurrence rates. The interesting feature in both these cases was their presentation with dyspepsia. Persistence of symptoms and normal upper gastrointestinal endoscopy directed attention to the presence of hyponatraemia that led to the diagnosis of panhypopituitarism due to Rathke's cleft cyst.

Case Reports

Case 1

A 56-year-old lady presented with nausea and occasional vomiting of one month's duration. There was no epigastric pain, haematemesis, melena or past peptic ulcer disease. She had diabetes mellitus and was on metformin 500 mg thrice daily. The physical examination was normal. The blood pressure (BP) was 120/80 mmHg. With an initial diagnosis of dyspepsia, she underwent an upper gastrointestinal endoscopy that revealed minimal gastritis.

* Consultant

Division of Endocrinology, Department of Medicine, National University Hospital

** Consultant Endocrinologist

Gleneagles Medical Centre

*** Senior Consultant and Head

Department of Neurosurgery, National Neuroscience Institute

**** Consultant and Head

Neuropathology Laboratory, National Neuroscience Institute

Address for Reprints: Dr J J Mukherjee, Division of Endocrinology, Department of Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

The rapid urease test for the detection of *Helicobacter pylori* (CLO-test) was negative. She was treated with cisapride and famotidine with no improvement in her symptoms. An ultrasound of the abdomen was normal. Further investigations revealed normal serum calcium, urea, creatinine and liver function tests. However, serum sodium was low at 128 mmol/L and she was referred to an endocrinologist for further management. There were no additional features in the history. In particular, there were no symptoms of headache or visual difficulties. She had continued to have regular periods till attaining menopause about 5 years ago. The only additional examination finding was of postural hypotension (lying and standing BP of 150/90 and 120/70 mmHg, respectively). Visual fields were normal by confrontation.

In view of symptoms of nausea and vomiting and presence of postural hypotension and hyponatraemia, hypoadrenalism needed exclusion. Serum cortisol measured at 8 am was low at 10 nmol/L and reached a peak of only 119 nmol/L at 60 minutes following the intravenous administration of 250 mcg of tetracosactrin.¹⁶ Plasma adrenocorticotrophic hormone (ACTH) was low at 7.3 ng/L (normal 10 to 40). This was consistent with deficiency of the hypothalamo-pituitary-adrenal (HPA) axis. Serum IGF1 was low at 77.4 ng/mL (normal 114 to 492), suggestive of growth hormone (GH) deficiency. Serum luteinizing (LH) and follicle stimulating hormone (FSH) levels, instead of the expected high levels in post-menopausal women, were low at 1.0 U/L and 4.5 U/L, respectively, confirming gonadotrophin deficiency. Free T4 was low at 7.51 pmol/L (10.3 to 31.0) with a TSH of 1.46 mu/L, consistent with secondary hypothyroidism. Serum prolactin was normal at 1.17 nmol/L (normal 0.03 to 1.20). There was no visual field deficit on formal visual perimetry. MRI of the pituitary showed a 0.8 x 0.5 cm cystic lesion in the sellar region with minimal suprasellar extension. There was no compression of the optic chiasm. The signal characteristics were reported to be suggestive of fluid (Figs. 1 and 2). She was commenced on replacement doses of oral hydrocortisone and thyroxine. With a preoperative diagnosis of probable Rathke's cleft cyst, she was referred for transsphenoidal surgery (TSS). At surgery, a small cyst containing mucoid fluid was found which was drained, and the cyst wall was partially excised. Histology showed remnants of a cyst partially lined by flattened-to-low cuboidal epithelium confirming the diagnosis of Rathke's cleft cyst. Postoperative MRI revealed disappearance of the cystic lesion from the sellar region. Postoperatively, she remained hypothyroid requiring 75 mcg of thyroxine daily. Serum IGF1 was low at 22.7 ug/L suggestive of continued GH deficiency. However, there was a complete recovery of her HPA axis with the 8 am cortisol being 363 nmol/L, rising to a peak of 994 nmol/L at 60 minutes following the intravenous administration of

250 mcg of tetracosactrin. There was a partial improvement in the gonadotrophin axis as well with the LH being measurable at 7.7 U/L and FSH at 26 U/L. She continues to remain free of recurrence with normal visual fields 21 months following surgery.

Case 2

A 69-year-old gentleman with history of chronic obstructive pulmonary disease (COPD) was admitted with complaints of epigastric discomfort and nausea. There was no history of haematemesis, melena or past peptic ulcer disease. The physical examination was normal except for findings consistent with COPD. The BP in supine position was 100/60 mmHg. The full blood count revealed an elevated eosinophil count at 13.8% with a normal white cell count of $5.9 \times 10^3/\mu\text{L}$. Serum sodium was low at 124 mmol/L. Free T4 was low at 8.01 pmol/L with a normal TSH at 1.61 mu/L. A diagnosis of dyspepsia was considered and he underwent an upper gastrointestinal endoscopy that was essentially normal. He was discharged on cisapride and famotidine. However, he was readmitted 3 days later with persistent epigastric discomfort, nausea and generalised weakness. The BP was low as before at 100/60 mmHg. An ultrasound of the abdomen was normal. Serum sodium was again low at 120 mmol/L. Serum osmolality was low at 250 Osm/kg with an elevated urine osmolality at 502 mOsm/kg. With a diagnosis of syndrome of inappropriate secretion of anti-diuretic hormone (SIADH), he was commenced on fluid restriction. A computed tomographic (CT) scan of the brain showed a small focal hypodensity in the left external capsule consistent with an old infarct, considered not to be a significant cause of his SIADH.

He was referred to an endocrinologist for further management of SIADH. It was then noted that persistent nausea, eosinophilia, hypotension, and low serum sodium and osmolality were all suggestive of hypoadrenalism. Moreover, the low free T4 and normal TSH recorded at his previous admission were suggestive of secondary hypothyroidism. Serum cortisol, measured at 8 am, was low at 142 nmol/L rising to a peak of 331 nmol/L at 60 minutes following the intravenous administration of 250 mcg of tetracosactrin, confirming hypoadrenalism. Serum IGF1 was low at 28.2 ug/L, suggestive of GH deficiency. Serum testosterone was low at <0.07 nmol/L with the LH and FSH at <0.1 U/L and 1.02 U/L, respectively, confirming gonadotrophin deficiency. Serum prolactin was mildly elevated at 902 mU/L. Visual field examination revealed bitemporal hemianopia. MRI of the pituitary fossa revealed a well-defined, 1.5 x 1.5 cm cystic sellar lesion, hypointense on T1 and hyperintense on T2 weighted imaging, extending into the suprasellar region and compressing the optic chiasm (Fig. 3). There was a thin rim of enhancement following contrast injection. The CT scan of the brain,



Fig. 1. Post contrast T1 weighted coronal image of the pituitary fossa shows the non-enhancing Rathke's cleft cyst (arrow).

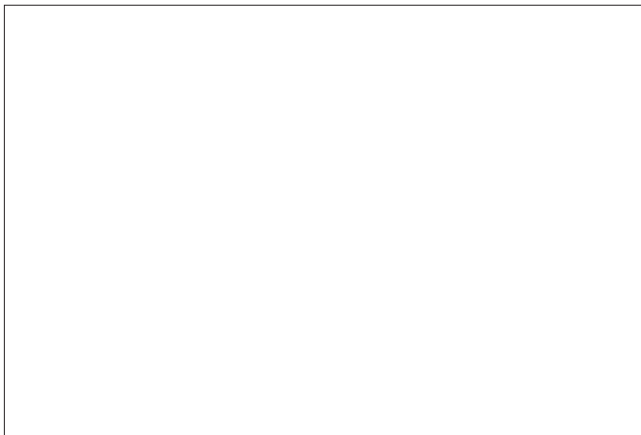


Fig. 2. Coronal T2 weighted image at the same level as in Figure 1 showing the lesion having a signal intensity of fluid (arrowhead), reflecting its cystic nature.

when reviewed, failed to show the lesion because the cuts through the sellar region were not fine enough to detect the cyst. A diagnosis of a cystic pituitary lesion, probable Rathke's cleft cyst with panhypopituitarism was considered. The mildly elevated serum prolactin was attributed to pituitary stalk compression by the cyst. He was commenced on replacement doses of hydrocortisone and thyroxine. His symptoms improved promptly following glucocorticoid replacement, as did the BP that stabilised at 120/80 mmHg. The hyponatraemia resolved.

He was referred for TSS. At operation, a cyst containing mucinous substance and scanty amount of solid tissue was found that was drained and the cyst wall was partially excised. Histology showed scanty fragments of ciliated cuboidal epithelium confirming the diagnosis of Rathke's cleft cyst. Two months following surgery, his visual fields had recovered. He refused further investigations including hormonal measurements and pituitary imaging. He was advised to continue on replacement doses of hydrocortisone, 75 mcg once daily of thyroxine and was commenced on testosterone undecanoate 40 mg thrice daily. He defaulted from further follow-up and presented 8 months later with



Fig. 3. Coronal post-contrast T1 weighted image showing a macroadenoma which has suprasellar extension (arrowhead). This has a "waist" (*) as it passes through the diaphragma sella, giving it a figure of 8 configuration.

symptoms of nausea, weakness and weight loss. The BP was low at 90/60 mmHg. On questioning, it became apparent that he had run out of hydrocortisone tablets for 4 to 6 weeks. A random cortisol measured prior to commencing intravenous hydrocortisone replacement was low at 88 nmol/L confirming hypoadrenalism. His symptoms and BP steadily recovered following hydrocortisone replacement. The thyroid functions were detected to be normal (Free T4 12.38 pmol/L and TSH 2.20 mu/L) despite him having stopped thyroxine replacement for the past few months. Visual fields by confrontation were noted to be normal. He refused pituitary imaging. He was discharged on replacement doses of hydrocortisone and testosterone undecanoate. DEXA-bone densitometry confirmed gross osteoporosis with the bone mineral density of the lumbar spine and the left hip (T-score) being 4.74 and 4.91 standard deviations, respectively, below the mean value in normal young men. He refused bisphosphonate therapy and was commenced on calcitriol along with calcium supplementation. When last reviewed 11 months following surgery, he was keeping well on replacement doses of hydrocortisone and testosterone undecanoate with no visual field deficit.

Discussion

Rathke's cleft cysts are believed to be derived from the remnants of Rathke's pouch, which forms as an outgrowth of the stomodeum during the 3rd or 4th week of gestation.^{7,12} The cranial elongation of the pouch forms the craniopharyngeal duct, the distal portion of which combines with the infundibular process of the neural tube. The anterior wall of the duct gives rise to the anterior lobe and pars tuberalis while the posterior wall forms the pars

intermedia of the pituitary gland. The lumen is obliterated by epithelial infoldings, failure of which leads to the formation of Rathke's cleft cyst. Some authors, however, believe that these cysts are derived directly from neuro-epithelium,^{17,18} endoderm¹⁹ or as a result of metaplasia of the anterior pituitary cells.²⁰

Symptomatic cysts are rare with less than 250 cases reported. A prevalence rate of approximately 1% amongst patients with pituitary and hypothalamic tumours has been documented.⁹ These cysts usually present as intrasellar lesions with approximately one-third having a significant suprasellar extension.²¹ However, various atypical presentations of Rathke's cleft cysts have been described including symptomatic hyponatraemia (similar to both our patients),²² entirely suprasellar location,²³ haemorrhage²⁴ and abscess^{25,26} within a Rathke's cleft cyst and in association with pituitary adenomas.²⁷

Agnetti et al²⁸ and others^{8,10,15} have noted a female preponderance amongst patients with symptomatic Rathke's cleft cysts while no definite sex difference has also been reported.^{3,9} The age at presentation has been quite variable, ranging from 4 to 73 years.⁸ Shanklin⁷ found a higher frequency in the second and third decades whilst Agnetti et al²⁸ reported a higher incidence in the fifth and sixth decades.²³ A more recent series noted a mean age of onset in the latter half of the third decade.¹⁰ Our patients were in their fifth and sixth decades.

The common presentations of symptomatic Rathke's cleft cysts include pituitary dysfunction, headache and, in the event of suprasellar extension, visual loss due to compression of the optic chiasm. Pituitary dysfunction has been noted in 66% to 81% and panhypopituitarism in 25% to 40% of patients.⁸⁻¹⁰ Diabetes insipidus at presentation has been seen in 13% to 17% and isolated hyperprolactinaemia in 7% to 17% patients.^{8,9} Both our patients had panhypopituitarism and presented dramatically with symptoms of adrenal insufficiency masquerading as gastrointestinal pathology. One of our patients had elevated serum prolactin as well but none had evidence of diabetes insipidus. Visual disturbance with field defects has been reported by 52% to 66% of patients and headache at presentation has been documented in 33% to 65% of patients.⁸⁻¹⁰ One of our patients had bitemporal hemianopia but none specifically complained of headache.

Although there have been numerous attempts to define the features of a Rathke's cleft cyst on pituitary imaging, there are no pathognomonic features that helps to distinguish it preoperatively from a craniopharyngioma. The cyst density on CT scanning and cyst intensity on MRI has been variably reported to range from hypo- to iso- to mixed density/intensity.^{5,29} Both our patients had a hypointense lesion on T1 and hyperintense lesion on T2 weighted

images consistent with that of fluid. Lack of post-contrast enhancement on MRI has been suggested by some to be the hallmark of these cysts,⁵ but patchy or ring enhancement post-gadolinium injection has also been reported as seen in the second patient in our series.¹⁵ A recent combined series comparing craniopharyngioma, Rathke's cleft cyst and intrasellar arachnoid cysts reported that intensity on CT or MR and the post-contrast enhancement pattern were unable to distinguish these lesions, whereas the presence of solid components, purely suprasellar location, presence of calcification and a size greater than 20 ± 5 mm in the greatest diameter favoured a craniopharyngioma.¹⁰ However, solid components have been reported in Rathke's cleft cysts as is a purely suprasellar location. Calcification, said to be characteristically absent from Rathke's cleft cysts, has also been seen in isolated cases.^{4,30}

Recurrence of Rathke's cleft cysts is rare. A review of the literature till 1996 revealed only 7 well-documented recurrences.⁹ However, a number of studies since then have reported on a higher incidence of recurrence. Mukherjee et al⁹ noted a recurrence in 4 out of 12 patients (33%) occurring 3 to 48 months after surgery, Shin et al¹⁰ in 5 out of 26 patients (19%) with a mean time to recurrence of 25 ± 19 months and Keyaki et al³¹ in 2 out of 12 patients (16.6%) at 6 and 65 months post surgery. Presence of a solid lesion within the cyst consisting of stratified squamous epithelium, dark cyst fluid, cholesterol crystals, multi-layered walls and larger size of the cyst have been reported to increase the risk of a recurrence^{3,10,14,32} However, recurrence of cysts lined by a single layer of cuboidal or columnar epithelium has also been reported.^{9,13,15} Fager and Carter³³ suggested that craniopharyngiomas and Rathke's cleft cysts have overlapping histological features, which is more obvious in the case of recurrent Rathke's cleft cysts. The optimal therapy for a recurrent symptomatic Rathke's cleft cyst remains unclear, but transsphenoidal aspiration and, where possible, extensive removal of the cyst wall is most appropriate; one group has followed repeat surgery with external beam pituitary radiotherapy but the role of radiotherapy in this situation is at best unclear.⁹ Careful follow-up following surgery is imperative and periodic neuro-ophthalmological examination and MRI, 6 and 12 months after surgery and at yearly intervals from then on for at least 5 years, has been recommended.⁹

In summary, we present 2 patients with symptomatic Rathke's cleft cyst who presented with "dyspeptic" symptoms. They were both subsequently noted to have persistent hyponatraemia and were detected to have ACTH deficiency. Further investigations revealed panhypopituitarism. MRI of the pituitary showed cystic sellar lesions, which on histology were Rathke's cleft cysts. There has been an improvement in the endocrine functions

in both and visual field defect in one patient following transsphenoidal surgery with drainage of the cyst and partial excision of the cyst wall.

Conclusions

Hyponatraemia is a common electrolyte abnormality and an accurate aetiological diagnosis is an essential prerequisite to appropriate therapy. It is obligatory to establish normal thyroid and hypothalamo-pituitary-adrenal function prior to attributing the aetiology of euvolaemic hyponatraemia to SIADH. On discovery of hypothalamo-pituitary-adrenal or hypothalamo-pituitary-thyroid axis dysfunction, it is essential to screen for abnormalities in the rest of the anterior pituitary functions followed by MRI of the pituitary fossa to exclude a sellar lesion. Symptomatic Rathke's cleft cysts are rare cystic sellar lesions that can present with pituitary dysfunction. Treatment of Rathke's cleft cysts involves transsphenoidal surgery with aspiration followed by partial excision of the cyst wall.

Acknowledgement

We would like to thank Dr Tan Tiong Yong, Consultant Radiologist, Changi General Hospital, Singapore for his help in choosing the MRI plates for print.

REFERENCES

1. Rasmussen A T. Ciliated epithelium and mucous-secreting cells in the human hypophysis. *Anat Rec* 1929; 41:273-83.
2. Russel D S, Rubinstein L J. Pathology of tumors of the nervous system. 4th ed. Baltimore: Williams & Wilkins, 1977:32-8.
3. Yoshida J, Kobayashi T, Kageyama N, Kanzaki M. Symptomatic Rathke's cleft cyst: morphological study with light and electron microscopy and tissue culture. *J Neurosurg* 1977; 47:451-8.
4. Nemoto Y, Inoue Y, Fukuda T, Shakudo M, Katsuyama J, Hakuba A, et al. MR appearance of Rathke's cleft cysts. *Neuroradiology* 1988; 30:155-9.
5. Sumida M, Uozumi T, Mukada K, Arita K, Kurisu K, Eguchi K. Rathke's cleft cysts: Correlation of enhanced MR and surgical findings. *Am J Neuroradiol* 1994; 15:525-32.
6. Gillman T. The incidence of ciliated epithelium and mucous cells in the normal Bantu pituitary. *S Afr J Med Sci* 1940; 5:30-40.
7. Shanklin W M. Incidence and distribution of cilia in the human pituitary with a description of micro-follicular cysts derived from Rathke's cleft. *Acta Anat* 1951; 11:361-82.
8. Voelker J L, Campbell R L, Muller J. Clinical, radiographic and pathological features of symptomatic Rathke's cleft cysts. *J Neurosurg* 1991; 74:535-44.
9. Mukherjee J J, Islam N, Kaltsas G, Lowe D G, Charlesworth M, Afshar F, et al. Clinical, radiological and pathological features of patients with Rathke's cleft cysts: Tumors that may recur. *J Clin Endocrinol Metab* 1997; 82:2357-62.
10. Shin J L, Asa S L, Woodhouse L J, Smyth H S, Ezzat S. Cystic lesions of the pituitary: Clinicopathological features distinguishing craniopharyngioma, Rathke's cleft cyst and arachnoid cyst. *J Clin Endocrinol Metab* 1999; 84:3972-82.
11. Brassier G, Morandi X, Tayiar E, Riffaud L, Chabert E, Heresbach N, et al. Rathke's cleft cysts: surgical-MRI correlation in 16 symptomatic cases. *J Neuroradiol* 1999; 26:162-71.
12. Berry R G, Schlezinger N S. Rathke's cleft cysts. *Arch Neurol* 1959; 1:48-58.
13. Raskind R, Brown H A, Mathis J. Recurrent cyst of the pituitary: 26-year-follow-up from first decompression. *J Neurosurg* 1968; 28:595-9.
14. Iraci G, Giordano R, Gerosa M, Rigobello L, Di Stefano E. Ocular involvement in recurrent cyst of Rathke's cleft—case report. *Ann Ophthalmol* 1979; 11:94-8.
15. Ross D A, Norman D, Wilson C B. Radiologic characteristics and results of surgical management of Rathke's cysts in 43 patients. *Neurosurgery* 1992; 30:173-9.
16. Trainer P J, Besser M, compilers. The Barts Endocrine Protocols. Edinburgh: Churchill Livingstone, 1995:52.
17. Shuangshoti S, Netsky M G, Nashold B S Jr. Epithelial cysts related to the sella turcica: Proposed origin from neuroepithelium. *Arch Pathol* 1970; 90:444-50.
18. Concha S, Hamilton B P M, Millan J C, Mcqueen J D. Symptomatic Rathke's cleft cyst with amyloid stroma. *J Neurol Neurosurg Psychiatry* 1975; 38:782-6.
19. Hirano A, Ghatak N R. The fine structure of colloid cysts of the third ventricle. *J Neuropathol Exp Neurol* 1974; 33:333-41.
20. Naiken V S, Tellem M, Meranze D R. Pituitary cyst of Rathke's cleft origin with hypopituitarism. *J Neurosurg* 1961; 18:703-6.
21. Rout D, Das L, Rao V R K, Radhakrishnan V V. Symptomatic Rathke's cleft cysts. *Surg Neurol* 1983; 19:42-5.
22. Nakayama Y, Tanaka A, Naritomi K, Yoshinaga S. Hyponatremia-induced metabolic encephalopathy caused by Rathke's cleft cyst: a case report. *Clin Neurol Neurosurg* 1999; 101:114-7.
23. Itoh J, Usui K. An entirely suprasellar symptomatic Rathke's cleft cyst: Case report. *Neurosurgery* 1992; 30:581-5.
24. Onesti S T, Wisniewski T, Post K D. Pituitary hemorrhage into a Rathke's cleft cyst. *Neurosurgery* 1990; 27:644-6.
25. Obenchain T G, Becker D P. Abscess formation in Rathke's cleft cyst—case report. *J Neurosurg* 1972; 36:359-62.
26. Sonntag V K H, Plenge K L, Balis M S, Raudzens P A, Hodak J A, Clark R J, et al. Surgical treatment of an abscess in a Rathke's cleft cyst. *Surg Neurol* 1983; 20:152-6.
27. Nishio S, Mizuno J, Barrow D L, Takei Y, Tindall G T. Pituitary tumors composed of adenohypophysial adenoma and Rathke's cleft cyst elements: A clinicopathological study. *Neurosurgery* 1987; 21:371-7.
28. Agnetti V, Carreras M, Rocca A, Turtas S, Viale G L. Epithelial cysts related to the Rathke's cleft. *J Neurosurg Sci* 1974; 18:65-9.
29. Kucharczyk W, Peck W W, Kelly W M, Norman D, Newton T H. Rathke's cleft cysts: CT, MR imaging, and pathologic features. *Radiology* 1987; 165:491-5.
30. Adelman L, Post K. Calcification in Rathke's cleft cyst. *J Neurosurg* 1977; 47:641.
31. Keyaki A, Kim Y J, Nabeshima S. Clinical study of symptomatic Rathke cleft cyst. *No Shinkei Geka* 1999; 27:625-31.
32. Eisenberg H M, Weiner R L. Benign pituitary cysts. In Wilkins R H, Rengachary S S, editors. *Neurosurgery*. New York: McGraw-Hill, 1985:932-4.
33. Fager C A, Carter H. Intracellular epithelial cysts. *J Neurosurg* 1966; 24:77-81.