

Case Report

Partially Reversible Hypopituitarism in an Adolescent with a Rathke Cleft Cyst

Carla Bizzarri¹, Romana Marini¹, Graziamaria Ubertini¹, and Marco Cappa¹

¹Unit of Endocrinology and Diabetes, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Abstract. Rathke cleft cysts are remnants of the Rathke pouch. Most of them are asymptomatic, but sometimes they can grow enough to cause compression of structures within and/or close to the sella, thus eliciting symptoms such as visual disturbance, pituitary defects, and headache. Asymptomatic cysts can safely be followed up with serial imaging, while the standard treatment for symptomatic lesions is surgical removal. We describe a 14-yr-old boy, admitted for anorexia, fatigue, weight loss, recurrent headache and vomiting. Magnetic resonance imaging showed an intra- and suprasellar cystic lesion, which was surgically removed. Histology was consistent with Rathke's cleft cyst. Diabetes insipidus and multiple anterior pituitary defects (GH, ACTH and TSH) were found preoperatively, and substitutive therapy was started. No additional hormonal defect appeared after surgery. After 4 yr of follow up, pituitary function was retested, and there were no confirmed GH or ACTH defects, allowing a partial withdrawal of replacement therapy. Our report confirms that pituitary defects, in patients with a Rathke cleft cyst, may recover even year after surgery. Thus, retesting of pituitary axes is indicated during long-term follow up.

Key words: Rathke cleft cyst, pituitary, GH

Introduction

The sellar region can be affected by a variety of cystic lesions, including neoplastic craniopharyngioma, non-neoplastic Rathke cleft cyst, and arachnoid cyst. Distinction among the different forms before surgery is often difficult, because the symptoms, signs, and biochemical and imaging features of these lesions can mimic each other (1). The pituitary gland is derived from two embryonic precursors: the anterior lobe originates from the Rathke pouch, an upgrowth

of ectoderm from the roof of the stomodeum (pharyngeal epithelium), whereas the posterior lobe (along with the rest of the diencephalon) originates from a downgrowth of the neuroectoderm. The Rathke pouch normally closes early during fetal development, but a remnant often persists as a Rathke cleft in the *pars intermedia* between the anterior and posterior lobes. Rathke cleft cysts are remnants of the Rathke pouch (2). Most of them are asymptomatic; they have been found incidentally in 4% to 33% of autopsies (3). Symptomatic cysts are uncommon in childhood and adolescence, but their prevalence increases slowly with age (3). Rathke cleft cysts can grow enough to cause compression of structures within and/or close to the sella, thus eliciting symptoms such as visual disturbance, headache and endocrine defects.

Received: June 4, 2012

Accepted: July 23, 2012

Correspondence: Dr. Carla Bizzarri, Unit of Endocrinology and Diabetes, Bambino Gesù Children's Hospital, P.zza S. Onofrio n. 4, 00165, Rome, Italy

E-mail: carla.bizzarri@opbg.net

Diabetes insipidus is the presenting feature in approximately 7–20% of patients, while preoperative anterior pituitary defects occur in 41% of adults and 45% of children. Hyperprolactinemia and growth hormone deficiency are more common, followed by central adrenal insufficiency and hypogonadism (4). Although asymptomatic cysts can safely be followed up with serial imaging, the standard treatment for symptomatic lesions is surgical removal, typically through a transsphenoidal approach.

Case Report

A 14-yr-old boy was admitted to our hospital for anorexia, progressive fatigue, weight loss, recurrent headache and vomiting. The symptoms had appeared gradually two months prior to admission and were progressively worsening. He was born from healthy unrelated Caucasian parents. His perinatal history was unremarkable, with a normal birth history, and normal motor and mental development. Physical assessment showed normal vital signs. The results of a neurological examination were normal. Pallor of the skin and mucous membranes and sunken eyes were evident. His weight, height and BMI were 49.4 kg (−0.76 SDS), 161.5 cm (−0.59 SDS) and 18.9 (−0.71 SDS), respectively. His pubertal stage was P2G2, according to Tanner, with a testicular volume of 8 ml bilaterally. The thyroid gland was not palpable. Considering the family's history of autoimmune thyroid disease, a general practitioner had ordered a basal evaluation of thyroid function a few days before admission that showed the following results: 1.44 μ IU/ml (nr: 0.4–5.5) TSH, 0.63 ng/dl (nr: 0.7–1.8) FT4, negative for anti-thyroperoxidase antibodies and negative for anti-thyroglobulin antibodies.

Results

Considering the low FT4 levels and the “inappropriately” normal TSH levels, which were

suggestive of secondary (central) hypothyroidism, we performed a morning fasting cortisol, ACTH, IGF-I, prolactin and DHEAS test, and the results were as follows: 2.95 mcg/dl (nr: 6–23), 10.8 pg/ml (nr: 5–55), 77.9 ng/ml (−2.48 SDS, according to age and gender), 28.84 ng/ml (nr: 1.0–20) and 308 ng/ml (350–4,300 ng/ml), respectively. A low dose ACTH stimulation test (Synacthen: 1 mcg intravenously) confirmed central adrenal insufficiency (5), with basal cortisol being 3 mcg/dl and 1-h post-ACTH cortisol being 15.9 mcg/dl (normal cortisol response >18 mcg/dl). An arginine stimulation test (0.5 g/kg arginine infused intravenously over 30 min) demonstrated a GH deficiency (GH peak: 0.91 ng/ml). A GnRH test (Lutrelif - Ferring 100 mcg intravenously) showed a relatively low gonadotrophin response for age and pubertal stage: LH peak, 3.4 mU/ml, FSH peak, 2.74 mU/ml, and testosterone level, 38.68 ng/dl. Bone age was 13 yr, according to the Greulich & Pyle standards. Fundoscopy, visual field and acuity tests were normal. He was started on hydrocortisone (6.7 mg/m²/d) and levothyroxine therapy (1 mcg/kg/d). Three weeks later, central diabetes insipidus clinically appeared with polyuria and polydipsia. His daily fluid intake was 7,000 ml (4,490 ml/m²) and daily urine output was 6,800 ml (4,360 ml/m²). Serum osmolality was 310 mOsm/kg with a concurrent urine osmolality of 54 mOsm/kg. Treatment with oral desmopressin (0.1 mg/dose, 3 times a day) was started and his water balance normalized in a few days.

Magnetic resonance imaging (MRI) showed a regularly shaped intra- and suprasellar cystic lesion extending up to the optic chiasm (cyst diameters: 17 × 12.4 × 14 mm). The lesion appeared hyperintense on T₁ and T₂ weighted images, and no contrast enhancement was observed. The pituitary gland and pituitary stalk were not clearly recognizable (Fig. 1).

Transsphenoidal surgery via a fully transnasal endoscopic approach was performed with total removal of the lesion (cyst evacuation combined with wall excision). The pituitary gland

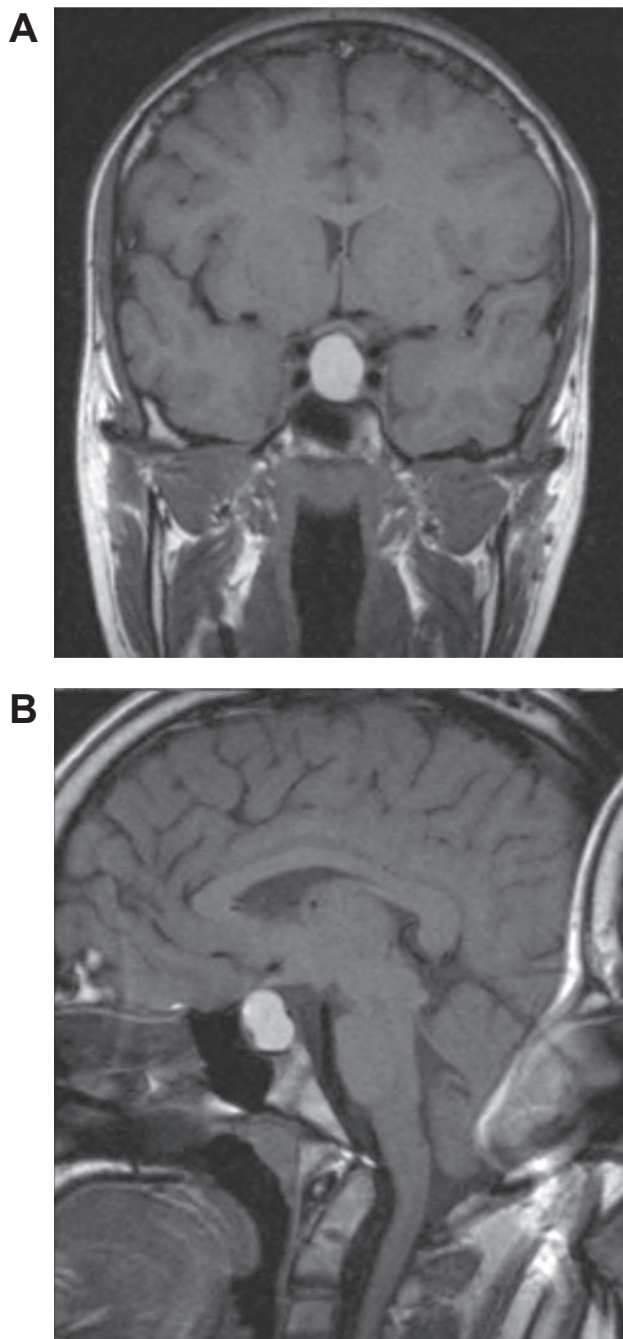


Fig. 1 Preoperative MRI (1A, coronal view; 1B, sagittal view) showing a regularly shaped intra- and suprasellar lesion that is hyperintense, homogeneous and not enhanced with contrast and involves the entire stalk, which cannot be distinguished from the posterior pituitary.

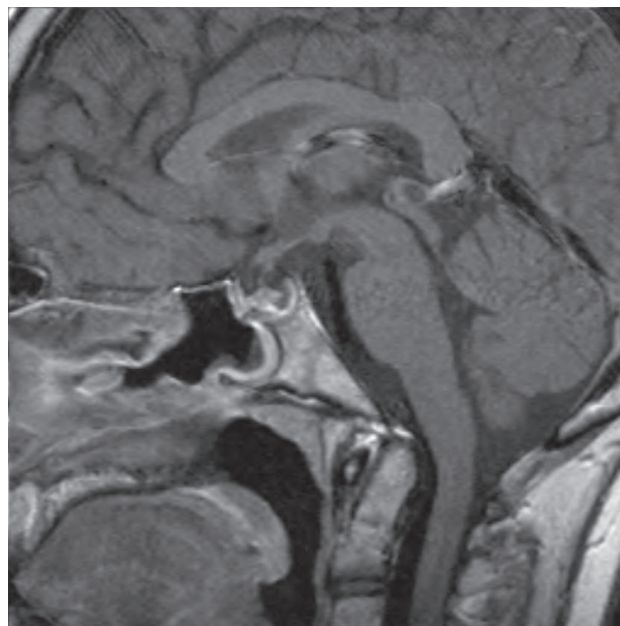


Fig. 2 Control MRI repeated 3 mo after surgery (sagittal view) showing a heterogeneous signal in the sellar area, mostly due to cerebrospinal fluid. The pituitary gland is poorly defined and flattened on the sellar floor. The pituitary stalk size and morphology are normal.

and stalk were preserved. No cerebrospinal fluid leak occurred during the procedure. The cyst content was found to be mucoid, and histological examination of the cyst wall revealed a single layer of well differentiated, cuboidal, ciliated, epithelial cells, without any evidence of squamous metaplasia. The histological diagnosis was consistent with a Rathke's cleft cyst. Three months after surgery, control MRI showed dishomogeneous materials in the sella, mostly cerebrospinal fluid. The pituitary gland was poorly defined and flattened on the sellar floor. The pituitary stalk appeared to be normal (Fig. 2).

Six months after surgery, a complete arrest of linear growth became evident, with the patient's height, weight and BMI being 161.5 cm (−1.1 SDS), 55 kg (−0.59 SDS) and 21.1 (−0.08 SDS), respectively. His prolactin level was: 21.8

ng/ml. A GHRH + arginine stimulation test was performed (1 mcg/kg GHRH administered by an intravenous bolus, followed by a 30-min infusion of 0.5 g/kg arginine), and it showed a persistent severe GH deficiency, with a GH peak of 1.72 ng/ml and IGF-I of 62 ng/ml (-2.57 SDS). A GnRH test showed a normal pubertal response for LH and FSH (LH peak of 7.7 mU/ml; FSH peak of 3.63 mU/ml). GH substitutive therapy was started at the dose of 0.20 mg/kg/wk, and he exhibited significant catch-up growth.

At the age of 17 yr, GH therapy was stopped. The calculated height velocity during the previous year was 0.6 cm/yr. His bone age, evaluated according to Greulich & Pyle standards, was 17 yr, and his final height was 169.5 cm (-1.02 SDS), with mid-parental height: 168 cm (-1.36 SDS). Pubertal development had spontaneously evolved up to Tanner stage 5, with a testicular volume >20 ml bilaterally. His bone mineral density was analysed by Dual-energy X-ray absorptiometry (DXA) and showed a good bone mass accrual with a lumbar spine Z score of -1 and a total body Z score of -0.1 .

At the age of 17.5 yr, the patient was still being treated with a relatively low dose of hydrocortisone (5 mg/m²/d), without any symptoms suggestive of cortisol deficiency, and his basal ACTH levels were found to be in the normal range (23.7 pg/ml). Thus, hydrocortisone therapy was gradually reduced up to a complete withdrawal over 6 wk. The patient remained in good condition, without any signs or symptoms suggestive of adrenal insufficiency. A few days after complete stopping of hydrocortisone therapy, his basal fasting cortisol level was 10 mcg/dl, with a concurrent ACTH level of 15.6 pg/ml.

At the age of 18 yr, the patient underwent hormonal retesting. His prolactin level was 7.69 ng/ml. A low dose ACTH test confirmed a normal adrenal response (basal cortisol of 14.3 mcg/dl; 1 h post-ACTH cortisol, 23.58 mcg/dl). The GH peak at the time of an insulin tolerance test (ITT: 0.1 U/kg of regular insulin administered by an intravenous bolus) was 5.76 ng/ml (normal

response for adult age > 3 ng/ml), while that after a GHRH + arginine test was 24 ng/ml (normal response for adult age > 9 ng/ml); the IGF-I level was 230 ng/ml, -1.6 SDS). All these data documented a normal GH secretion for adult age (6). The cortisol peak during insulin tolerance test was 21 mcg/dl. Table 1 and Fig. 3 summarize the time course of the different hormonal data and GH response in the different stimulation tests performed over time, respectively.

Our patient is now 19 yr old, he is studying at a university with very good progress, and his performance in daily activities and sports is reported to be completely normal. During the 5-yr follow up period, serial control MRIs have shown no recurrence of the sellar lesion. Low FT4 levels (0.61 ng/dl), consistent with persistent hypothyroidism, were found at the end of a short trial off levothyroxine therapy. The patient reports the prompt recurrence of polyuria and polydipsia, whenever desmopressin intake is delayed, confirming permanent central diabetes insipidus.

Discussion

Patients with sellar lesions frequently present with pituitary hormone deficiencies (1, 7). Different studies have found preoperative endocrine dysfunction in 40–80% of patients with a symptomatic Rathke cleft cyst, with a variable proportion of patients showing improvement of pituitary function after surgery (1, 7–11). Jahangiri *et al.* (8) described that 45% of patients had preoperative hypopituitarism in a series of 14 children with symptomatic cysts and that 40% of these children experienced normalization of at least one pituitary axis postoperatively. None of the 3 children with growth arrest at clinical presentation resumed growth postoperatively, and none of the 3 patients who presented with low GH and IGF-I levels without growth arrest showed normalization of laboratory values after surgery. No child had new low GH or IGF-I levels postoperatively.

Table 1 Time course of the different hormonal data

	Diagnosis (age: 14 yr)	6 mo after surgery (age: 14.5 yr)	4 yr after surgery (age: 18 yr)
TSH (microUI/ml)	1.44	<0.15*	0.81*
FT4 (ng/dl)	0.63	0.96*	1.48*
IGF-I (ng/ml)	77.9	62	230
PRL (ng/ml)	28.84	21.8	7.69
Basal cortisol (mcg/dl)	3	–	14.3
post ACTH cortisol (mcg/dl)	15.9	–	23.58
Arginin test: GH peak (ng/ml)	0.91	–	–
Arginin + GHRH test: GH peak (ng/ml)	–	1.72	24
ITT: GH peak (ng/ml)	–	–	5.76
Basal LH (mU/ml)	1.7	3.6	5.5
GnRH test: LH peak (mU/ml)	3.4	7.7	–
Basal FSH (mU/ml)	1.94	2.82	7.8
GnRH test: FSH peak (mU/ml)	2.74	3.63	–
Testosterone (ng/dl)	38.68	101.81	512.6

*On levothyroxine therapy.

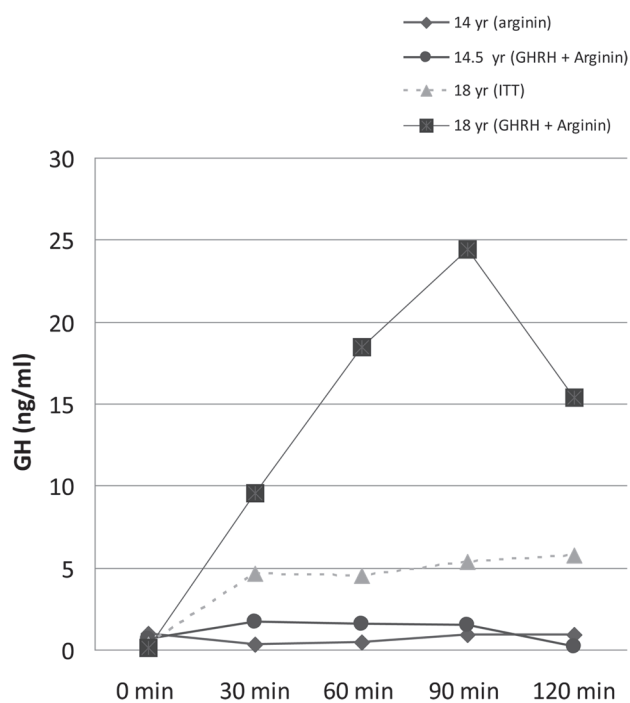


Fig. 3 GH response in the different stimulation tests performed before surgery (14 yr of age), 6 mo after surgery (14.5 yr of age) and 1 yr after the end of GH substitutive therapy (18 yr of age).

Zada *et al.* (9), in their retrospective review of 10 paediatric cases of Rathke cleft cyst, reported that 6/10 children demonstrated pituitary dysfunction before surgery, including GH deficiency (2 children), hyperprolactinemia (1 child), GH deficiency plus hyperprolactinemia (1 child), central adrenal insufficiency (1 child), and central adrenal insufficiency plus hypothyroidism (1 child). After surgery, 3 children developed new anterior pituitary deficits. In contrast with the previous study, the child with GH deficiency plus hyperprolactinemia in the present report showed a complete resolution of the hormonal defects.

To our knowledge, none of the reported studies (1, 7–11) analyzed how long after surgery the improvement of pituitary function was detected in hormonal laboratory tests. In our patient, a biochemical GH deficiency was already evident at the time of the clinical manifestation of the cyst, even though no recent history of growth deceleration was reported. No new hormonal defect became evident after surgery, but a persistent and severe GH deficiency, with clinically evident growth arrest, was confirmed 6 mo after surgery, and GH substitutive therapy

was needed to obtain a normal catch-up growth. Preoperative gonadotrophin levels were found to be relatively low but normalized completely after surgery, and the progression of puberty was normal. Unexpectedly, a late normalization of GH and ACTH secretion was found at the retesting performed after the attainment of final height, although we cannot exclude an earlier normalization during the years of substitutive therapy. On the other hand, pituitary axes are not investigable during substitutive therapy, and temporary interruptions of therapy are stressful and may be dangerous in childhood and adolescence. For these reasons hormonal retesting is usually performed after the completion of growth.

Hypopituitarism is usually considered to be permanent in patients with childhood-onset disease due to organic (congenital or acquired) pituitary lesions. In these patients, the need to confirm the hormonal defects, in particular GH deficiency, by retesting early in adult age is still debated (12). Our report confirms previous data indicating that pituitary defects, in patients with Rathke cleft cyst, are mainly related to chronic compression of the gland by the cyst and may be partially reversible after surgery (10, 11). The chance of recovery and the time interval between surgery and recovery could be variable in patients with Rathke cleft cysts, probably depending on lesion extension and type of surgical intervention. For these reasons, retesting of pituitary axes should be mandatory in patients with hypopituitarism related to a symptomatic Rathke cleft cyst removed during childhood.

References

1. Shin JL, Asa SL, Woodhouse LJ, Smyth HS, 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.
2. Voelker JL, Campbell RL, Muller J. Clinical, radiographic, and pathological features of symptomatic Rathke's cleft cysts. *J Neurosurg* 1991;74:535–44.
3. Teramoto A, Hirakawa K, Sanno N, Osamura Y. Incidental pituitary lesions in 1,000 unselected autopsy specimens. *Radiology* 1994;193:161–4.
4. Eguchi K, Uozumi T, Arita K, Kurisu K, Yano T, Sumida M, *et al.* Pituitary function in patients with Rathke's cleft cyst significance of surgical management. *Endocr J* 1994;41:535–40.
5. Maghnie M, Uga E, Temporini F, Di Iorgi N, Secco A, Tinelli C, *et al.* Evaluation of adrenal function in patients with growth hormone deficiency and hypothalamic-pituitary disorders: comparison between insulin induced hypoglycemia, low-dose ACTH, standard ACTH and CRH stimulation tests. *Eur J Endocrinol* 2005;152:735–41.
6. Biller BM, Samuels MH, Zagar A, Cook DM, Arafah BM, Bonert V, *et al.* Sensitivity and specificity of six tests for the diagnosis of adult GH deficiency. *J Clin Endocrinol Metab* 2002;87:2067–79.
7. Savas Erdeve S, Ocal G, Berberoglu M, Siklar Z, Hacıhamdioglu B, Evliyaoglu O, *et al.* The endocrine spectrum of intracranial cysts in childhood and review of the literature. *J Pediatr Endocrinol Metab* 2011;24:867–75.
8. Jahangiri A, Molinaro AM, Tarapore PE, Blevins L Jr, Auguste KI, Gupta N, *et al.* Rathke cleft cysts in pediatric patients: presentation, surgical management, and postoperative outcomes. *Neurosurg Focus* 2011;31:E3.
9. Zada G, Ditty B, McNatt SA, McComb JG, Krieger MD. Surgical treatment of Rathke cleft cysts in children. *Neurosurgery* 2009;6:1132–7.
10. Park JK, Lee EJ, Kim SH. Optimal surgical approaches for Rathke cleft cyst with consideration of endocrine function. *Neurosurgery* 2012;70(Suppl):250–6.
11. Wait SD, Garrett MP, Little AS, Killory BD, White WL. Endocrinopathy, vision, headache, and recurrence after transsphenoidal surgery for Rathke cleft cysts. *Neurosurgery* 2010;67:837–43.
12. Ghigo E, Aimaretti G, Corneli G. Diagnosis of adult GH deficiency. *Growth Horm IGF Res* 2008;18:1–16.