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An Unusual Presentation of Pediatric Cushing Disease: Recurrent Corticotropinoma of the Posterior Pituitary Lobe

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Abstract

Cushing's syndrome (CS) is rare in childhood and adolescence and its diagnosis and work up are often challenging. We report the case of a 15-year-old girl with a recurrent corticotrophin (ACTH)-secreting adenoma, located in the posterior lobe of the pituitary gland. At the age of 11, she presented with classic CS symptoms; biochemical investigation was compatible with ACTH-dependent Cushing disease, although pituitary gland imaging did not show any tumor. Following transsphenoidal surgery (TSS), histopathological analysis identified an ACTH-secreting pituitary microadenoma arising from the posterior gland. The patient went into remission but 4 years later she presented with recurrent CS; this time, pituitary gland imaging showed a microadenoma located in the posterior lobe, which was resected after TSS. Posterior lobe pituitary adenomas are very rare and often hard to diagnose and treat; this is the first case of such a tumor causing recurrent Cushing's disease in a child.

Keywords

Cushing disease; pituitary adenoma; microadenoma

INTRODUCTION

Cushing's syndrome (CS) is rare in children and adolescents. Pituitary corticotropin (ACTH)-secreting adenomas cause Cushing disease (CD) and account for more than 75% of the cases of CS in pediatrics^{1, 2}. In the majority of these cases, the tumor is small (almost always a microadenoma) and located in the anterior lobe of pituitary gland³.

Transsphenoidal surgery (TSS) is the treatment of choice^{1, 2, 4–8} and selective resection of the adenoma results in remission of CD in most patients^{9, 10}. To the best of our knowledge,

only a few cases of pituitary ACTH-producing adenomas entirely contained in the posterior lobe in adult CD patients have been described; recurrence of these tumors that are typically very small and thus easy to remove entirely, has not been reported^{11–13}. We describe the case of a female adolescent patient whose tumor was in the posterior pituitary lobe, as found in her first TSS. Although she was considered cured, four years later, CD recurred and she had to undergo a second TSS.

CASE REPORT

An 11-year-old Brazilian girl was referred to the National Institutes of Health (NIH) Clinical Center in 2005 because of clinical signs suggestive of Cushing's syndrome, including weight gain and decreasing growth rate. At the time of her admission she presented with short stature, obesity, facial plethora, hirsutism and acne. Her bone density was within normal limits (Z-score at the spine -0.5 and at the hip -0.5) and serum electrolytes and fasting blood glucose levels were normal. 24-hour urinary-free cortisol excretion (UFC) concentrations were markedly elevated, ranging from 463 to 854 micrograms/24 hours (normal range: 8 – 77). ACTH serum levels were 33.8 pg/mL (normal range: 4.9 – 46) and 24-hour 17-hydroxy steroids were also elevated at 16.9 to 24.1 mg per 24 hours (normal range: 2 – 6). Ovine CRH (oCRH) stimulation test showed a baseline ACTH of 46 pg/mL (normal range: 4.9 – 46) and a peak ACTH of 125 pg/mL and a baseline cortisol of 15.5 $\mu\text{g/dL}$ (normal range: 5 – 25) with a peak cortisol of 38.8 $\mu\text{g/dL}$. TSH and free T4 serum levels were normal, while FSH and LH were undetectable and estradiol levels were less than 10 pg/mL. Magnetic resonance imaging (MRI) of the pituitary gland performed on a 3 tesla (3 T) scanner showed very slight asymmetry of the gland, with the right side being slightly more prominent than the left (Fig. 1a and b). Bilateral inferior petrosal sinus sampling (BIPSS) showed an inferior petrosal sinus (IPS)-to-peripheral ACTH ratio (IPS/P) of 2.89 at baseline and of 15 after CRH infusion. TSS was performed. An adenoma was found in the posterior lobe of the pituitary gland, and most of the posterior pituitary tissue was resected. Histological investigation confirmed the diagnosis of an ACTH-producing pituitary adenoma located in the posterior lobe (Fig. 1c and d). The patient developed diabetes insipidus (DI) postoperatively and was started on vasopressin treatment. After surgery, the patient's baseline serum cortisol levels decreased to undetectable levels. Hydrocortisone (HC) replacement was initiated for adrenal insufficiency. No evidence of central hypopituitarism was observed. UFC levels were normal at the one year-follow-up appointment, at which point HC had been discontinued. Growth hormone (GH) deficiency was diagnosed 6 months after surgery and the patient underwent GH replacement therapy for 3 years. The patient started menstruating a year after TSS and completed puberty normally.

In 2009, at the age of 15, the patient was readmitted to our hospital because of apparent recurrence of CS: weight gain, irregular menses, and increased acne. UFC levels were elevated, ranging from 340 to 929 micrograms/24 hours (normal range: 8 – 77). Serum ACTH was 60 pg/mL. oCRH stimulation testing showed a baseline ACTH of 30.3 pg/mL (normal range: 4.9 – 46) and a peak ACTH of 54.5 pg/mL and a baseline cortisol of 19.8 $\mu\text{g/dL}$ (normal range: 5 – 25) with a peak cortisol of 28.1 $\mu\text{g/dL}$. MRI of the pituitary gland (3 T scanner) showed a region of hypoenhancement in the posterior lobe extending into the

thickened pituitary stalk (Fig. 2a and 2b). A second TSS was performed. Two nodules, one located in the pituitary stalk and the other in the posterior lobe attached to the adjacent dura mater, were found. Histologically, the specimens were described as a proliferation of somewhat pleomorphic anterior pituitary cells with expression of ACTH, in a pattern very similar to the one observed on specimens from the previous surgery (Fig. 2c and d). Postoperatively, the patient's cortisol serum levels dropped to less than 1 µg/dL and CRH stimulation testing showed a baseline ACTH of 5.0 pg/mL with a peak of 11.2 pg/mL and a baseline cortisol of less than 1.0 µg/dL with a peak of 2.9 µg/dL. UFC levels were undetectable after TSS. The patient has DI and remains on vasopressin replacement to date, but no other pituitary deficiencies have developed.

DISCUSSION

Diagnosis of CS and differential diagnosis of CD require a combination of laboratory tests and radiologic examinations^{14, 15, 16}. To distinguish CS from normal individuals and patients with pseudo-Cushing's states, the recommended screening tests include UFC and an overnight low-dose dexamethasone suppression test (DST). Once the diagnosis of CS is established, differentiation between its three forms starts with measurements of serum ACTH levels. If ACTH is not suppressed, ACTH-dependent causes should be investigated with the high-dose DST and oCRH testing. If these tests suggest a pituitary tumor, MRI imaging is recommended. BIPSS is useful in patients with ACTH-dependent CS whose clinical, biochemical or radiological studies are discordant or equivocal.

During childhood and adolescence, CS is very rare and the commonest form is a corticotropinoma, which accounts for 75% of the cases. The pituitary tumor is almost always a microadenoma¹⁷ and thus difficult to visualize on MRI. In general, adenomas are isointense or hypointense relative to gray matter on T1-weighted imaging, and isointense to slightly hyperintense on T2-weighted imaging, with a contrast-enhancement typically less intense than in the normal parenchyma of the anterior gland, in the early postinjection period. ACTH-secreting adenomas tend to be extremely small-sized, so 3 T scanners are better than the traditional imaging at 1.5 T, because the former can disclose very small lesions located in the anterior pituitary¹⁸. In contrast to microadenomas within the anterior lobe, neither the intermediate lobe nor the posterior lobe enhances with contrast on MRI, which makes the diagnosis of the posterior lobe tumors a great challenge, once most of them are not visible on MRI.

Pituitary tumors arise almost exclusively in the anterior lobe, which is embryologically and functionally distinct from the posterior lobe or neurohypophysis¹⁸. The anterior lobe is further comprised of the *pars distalis*, which forms the most the anterior lobe, the *pars tuberalis*, which partially envelopes the inferior stalk, and the *pars intermedia*, which correlates to the intermediate lobe in lower animals and may secrete proopiomelanocortin (POMC) in the younger population, but appears to involute by adulthood^{18, 19}.

We describe a young patient who presented with clinical and biochemical evidence of CD due to a corticotropinoma of the neurohypophysis. ACTH-producing adenomas can rarely arise completely within the posterior lobe. In 1934, Harvey Cushing described a posterior

lobe basophilic adenoma in a patient with CD¹². Additionally, another similar case was briefly reported by Boggan et al. in 1983¹¹. More recently, a description of 12 patients with CD, ACTH-secreting adenomas located wholly within the posterior lobe of the pituitary gland, pointed to the importance of the recognition of the posterior lobe as a possible, although uncommon, source for these adenomas¹³. In this series, four out of the 12 patients, which were treated at the NIH between 1992 and 2003, were children and no recurrence was observed after a mean follow-up of 71.9 months¹³. Long-term remission of pediatric CD varies widely from center to center as it is directly related to the appropriateness of the treatment. A complete resection of the tumor can produce remission in up to 97% of the cases^{1, 2, 7, 8}. Several diagnostic modalities have been used to predict recurrence, including measurements of serum cortisol or ACTH, UFC, low-dose dexamethasone suppression test and the oCRH stimulation test, all with varying success^{9, 10, 20}. In the patient we describe, recurrence was observed four years after TSS.

The developmental origin of tumors arising within the posterior lobe is still unclear. In horses and dogs, CD appears to be almost always the result of ACTH hypersecretion from the intermediate lobe^{21, 22}. In 1982, Lamberts et al. proposed that a subgroup of human corticotroph adenomas also arise from that lobe²³. A larger study from McNicol et al. did not support this hypothesis²⁴. We cannot exclude the possibility that in our patient, the origin of her tumor was in the intermediate lobe.

In conclusion, we describe the first pediatric patient with recurrent posterior lobe corticotropinoma, a tumor that is both rare and hard to identify. Clinicians taking care of children with CD should be aware of this unusual case of a pituitary lesion.

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References

1. Magiakou MA, Mastorakos G, Oldfield EH, et al. Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. *N Engl J Med*. 1994; 331:629–36. [PubMed: 8052272]
2. Storr HL, Chan LF, Grossman AB, Savage MO. Paediatric Cushing's syndrome: epidemiology, investigation and therapeutic advances. *Trends Endocrinol Metab*. 2007; 18:167–74. [PubMed: 17412607]
3. Ratliff JK, Oldfield EH. Multiple pituitary adenomas in Cushing's disease. *J Neurosurg*. 2000; 93:753–61. [PubMed: 11059654]
4. Das NK, Lyngdoh BT, Bhakri BK, et al. Surgical management of pediatric Cushing's disease. *Surg Neurol*. 2007; 67:251–7. discussion 7. [PubMed: 17320630]
5. Hofmann BM, Hlavac M, Martinez R, Buchfelder M, Muller OA, Fahlbusch R. Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years. *J Neurosurg*. 2008; 108:9–18. [PubMed: 18173305]
6. Joshi SM, Hewitt RJ, Storr HL, et al. Cushing's disease in children and adolescents: 20 years of experience in a single neurosurgical center. *Neurosurgery*. 2005; 57:281–5. discussion -5. [PubMed: 16094156]
7. Kanter AS, Diallo AO, Jane JA Jr, et al. Single-center experience with pediatric Cushing's disease. *J Neurosurg*. 2005; 103:413–20. [PubMed: 16302612]

8. Styne DM, Grumbach MM, Kaplan SL, Wilson CB, Conte FA. Treatment of Cushing's disease in childhood and adolescence by transsphenoidal microadenectomy. *N Engl J Med.* 1984; 310:889–93. [PubMed: 6321987]
9. Chen JC, Amar AP, Choi S, Singer P, Couldwell WT, Weiss MH. Transsphenoidal microsurgical treatment of Cushing disease: postoperative assessment of surgical efficacy by application of an overnight low-dose dexamethasone suppression test. *J Neurosurg.* 2003; 98:967–73. [PubMed: 12744355]
10. Hammer GD, Tyrrell JB, Lamborn KR, et al. Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. *J Clin Endocrinol Metab.* 2004; 89:6348–57. [PubMed: 15579802]
11. Boggan JE, Tyrrell JB, Wilson CB. Transsphenoidal microsurgical management of Cushing's disease. Report of 100 cases. *J Neurosurg.* 1983; 59:195–200. [PubMed: 6306181]
12. Cushing H. Hyperactivation of the Neurohypophysis as the Pathological Basis of Eclampsia and Other Hypertensive States. *Am J Pathol.* 1934; 10:145–76 31. [PubMed: 19970134]
13. Weil RJ, Vortmeyer AO, Nieman LK, Devroom HL, Wanebo J, Oldfield EH. Surgical remission of pituitary adenomas confined to the neurohypophysis in Cushing's disease. *J Clin Endocrinol Metab.* 2006; 91:2656–64. [PubMed: 16636117]
14. Arnaldi G, Angeli A, Atkinson AB, et al. Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab.* 2003; 88:5593–602. [PubMed: 14671138]
15. Vilar L, Freitas MC, Naves LA, et al. The role of non-invasive dynamic tests in the diagnosis of Cushing's syndrome. *J Endocrinol Invest.* 2008; 31:1008–13. [PubMed: 19169058]
16. Pivonello R, De Martino MC, De Leo M, Lombardi G, Colao A. Cushing's Syndrome. *Endocrinol Metab Clin North Am.* 2008; 37:135–49. ix. [PubMed: 18226734]
17. Kunwar S, Wilson CB. Pediatric pituitary adenomas. *J Clin Endocrinol Metab.* 1999; 84:4385–9. [PubMed: 10599692]
18. Delman BN. Imaging of pediatric pituitary abnormalities. *Endocrinol Metab Clin North Am.* 2009; 38:673–98. [PubMed: 19944287]
19. Mehta A, Dattani MT. Developmental disorders of the hypothalamus and pituitary gland associated with congenital hypopituitarism. *Best Pract Res Clin Endocrinol Metab.* 2008; 22:191–206. [PubMed: 18279788]
20. Batista DL, Oldfield EH, Keil MF, Stratakis CA. Postoperative testing to predict recurrent Cushing disease in children. *J Clin Endocrinol Metab.* 2009; 94:2757–65. [PubMed: 19470618]
21. Halmi NS, Peterson ME, Colurso GJ, Liotta AS, Krieger DT. Pituitary intermediate lobe in dog: two cell types and high bioactive adrenocorticotropin content. *Science.* 1981; 211:72–4. [PubMed: 6255564]
22. Orth DN, Holscher MA, Wilson MG, Nicholson WE, Plue RE, Mount CD. Equine Cushing's disease: plasma immunoreactive proopiomelanocortin peptide and cortisol levels basally and in response to diagnostic tests. *Endocrinology.* 1982; 110:1430–41. [PubMed: 6277607]
23. Lamberts SW, de Lange SA, Stefanko SZ. Adrenocorticotropin-secreting pituitary adenomas originate from the anterior or the intermediate lobe in Cushing's disease: differences in the regulation of hormone secretion. *J Clin Endocrinol Metab.* 1982; 54:286–91. [PubMed: 6274899]
24. McNicol AM, Teasdale GM, Beastall GH. A study of corticotroph adenomas in Cushing's disease: no evidence of intermediate lobe origin. *Clin Endocrinol (Oxf).* 1986; 24:715–22. [PubMed: 3024871]

Fig. 1.

Coronal (Panel a) and sagittal (Panel b) post contrast T1-weighted MRI scan of the pituitary obtained prior to the first surgery. The pituitary gland is normal in size and no definite adenoma is demonstrated. On the coronal images the central part of the pituitary enhances more intensely. This is a normal finding due to vascular tufts of the portal venous system projecting into the pituitary tissue from the adjacent stalk. Panels c and d show the hematoxylin and eosin and the ACTH-staining, respectively, in the posterior lobe pituitary tumor that was finally identified at surgery in this patient.

Fig. 2.

Panels a and b show, respectively, coronal and sagittal post contrast T1-weighted MRI scan of the pituitary obtained prior to the second surgery. The pituitary is smaller in size and its internal architecture distorted. An oval shaped hypoenhancing lesion is identified in the expected position of the posterior lobe (arrows). This abnormality also extends onto the adjacent stalk. A recurrent adenoma was found at surgery at this location. Panels c and d show the hematoxylin and eosin and the ACTH-staining, respectively, in the recurrent tumor.