Clinical Case Reports

WILEY

Clinical Case Reports Open Access

CASE REPORT OPEN ACCESS

A Rare Case of ACTH-Secreting Pituitary Adenoma in a Pediatric Patient. Diagnosis and Management: Case Report and Literature Review

Shadi Niliyeh[1] | Fatemeh Sayarifard[1] | Ali Moradi[2] | Aria Setoodeh[3] | Pouya Ebrahimi[4]

[1]Pediatric Endocrinology, Fellow, Children's Medical Center, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran | [2]Center for Translational Medicine, Faculty of Medicine, Semmelweis University, Budapest, Hungary | [3]Growth and Development Research Center, Children's Medical Center, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran | [4]Cardiology Department, Tehran Heart Center, Cardiovascular Disease Research Institute, Tehran University of Medical Sciences, Tehran, Iran

Correspondence: Aria Setoodeh (arset59@yahoo.com)

Received: 25 July 2024 | **Revised:** 14 March 2025 | **Accepted:** 23 March 2025

Funding: The authors received no specific funding for this work.

Keywords: adrenocorticotropic hormone | Cushing disease | endocrinology | pediatrics | pituitary adenoma

ABSTRACT

Due to its rare incidence, pituitary adenoma requires high vigilance and suspicion. Therefore, physicians should consider this differential diagnosis and perform the necessary workup, such as an overnight or standard dexamethasone suppression test and brain magnetic resonance imaging (MRI), to rule it out if sudden hormonal changes without any other explanation are observed in children.

1 | Introduction

The pituitary gland is inferior to the hypothalamus and superior to the optic chiasm [1]. Pituitary adenomas are predominantly benign tumors from various cell types, mostly from the adenohypophysis. The adenomas can be nonfunctional or functional. The nonfunctional type will only have mass effects, which present with neurological symptoms such as headaches and visual changes due to the compression of the optic chiasm; however, functional tumors can have both mass effects and hormone hypersecretion. As the patients with functional adenomas present to the clinic due to hormonal symptoms, the adenoma will not have sufficient time to grow and cause neurological symptoms [2]. Pituitary adenomas have a prevalence rate of 17% in the average population. However, they are extremely rare in children and adolescents, with a prevalence rate of around 3% and approximately 6% of brain tumors in the pediatric population. Among all the pituitary adenomas, prolactinomas are the most common, and adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas are rare [3–5]. An ACTH-secreting pituitary adenoma is a sporadic pituitary adenoma in children that can present with Cushing's syndrome symptoms, and according to prior studies, an ACTH-secreting pituitary adenoma is more common in girls than boys [5]. In this study, we present an extremely rare case of a six-year-old male patient without any past medical history who presented to the clinic with central obesity, increased hair growth, and mood change and was diagnosed with Cushing's disease. The magnetic resonance imaging (MRI) confirmed an ACTH-secreting pituitary adenoma, and he was treated with surgery accordingly. This study stresses the importance of diagnosing and managing this rare condition, which can have severe consequences and complications.

Abbreviations: ACTH, adrenocorticotropic hormone; BMI, body mass index; CBC, complete blood count; CMP, comprehensive metabolic panel; DI, diabetes insipidus; FSH, follicle-stimulating hormone; IGF1, insulin-like growth factor 1; IHC, immunohistochemistry; LH, luteinizing hormone; MEN1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; T4, thyroxine; TSH, thyroid-stimulating hormone; TSS, transsphenoidal surgery.

2 | Case Presentation

2.1 | Case History and Physical Exam

A six-year-old male patient presented to the outpatient clinic of a children's medical center affiliated with the Tehran University of Medical Science with his parents with the chief complaint of excessive hair growth over the body and weight gain, mainly in the abdomen, and change in mood for the past 2 months. The patient also complained of occasional headaches, but no other neurological symptoms, such as changes in vision, were reported. The patient's older brother was healthy and had no significant family history. In the physical examination, the moon's facial appearance, buffalo hump, hypertrichosis, and hirsutism over the body were observed. The patient's Tanner stage was prepubertal (Stage 1), height 105 cm, weight 27.8 kg, and body mass index (BMI) 24 kg/m^2, above the 95th percentile. The family denied taking or using any medication, such as oral medicine and creams, including cortisol-containing ones, such as herbal medications and over-the-counter medications.

2.2 | Methods

The initial laboratory tests, such as a complete blood count (CBC), comprehensive metabolic panel (CMP), lipid panel, thyroid function tests, urine analysis, and hormone assay performed by the electrochemiluminescence method, were done (Table 1). Based on the patient's chief complaint, symptoms during the physical examination, and laboratory results, which showed the level of ACTH and 8 a.m. cortisol higher than normal, the physicians suspected that Cushing's disease might be the cause of signs and symptoms, and the follow-up laboratory results were requested. Based on the patient's chief complaint, symptoms during the physical examination, and laboratory results, which showed the level of ACTH and 8 a.m. cortisol higher than normal, the physicians suspected that Cushing's disease might be the cause of signs and symptoms, and the follow-up laboratory results were requested.

The overnight dexamethasone suppression test was administered as directed: 1 mg of dexamethasone was given to the patient at 11 p.m., and blood was drawn at 8 a.m. the following day after the dexamethasone injection (Table 2). The next day, following the overnight dexamethasone suppression test, the standard procedure consists of administering 0.5 mg of oral dexamethasone every 6 h for 48 h. Blood was drawn to measure ACTH and cortisol levels (Table 3). Brain magnetic resonance imaging (MRI) was performed with and without gadolinium contrast.

The brain MRI with and without gadolinium contrast (Figure 1) revealed a well-defined 12 × 8 mm T1 hypointense lesion at the posterior portion of the anterior pituitary gland with mild contrast enhancement. The lesion has no mass effect on the optic chiasm. Also, a small area of T2 hyperintensity in the white matter of the right parietal lobe was reported, which could be due to gliosis after previous trauma or infection. With the impression of ACTH-secreting adenoma of the pituitary gland, transsphenoidal surgery (TSS) was done by a neurosurgery consultant, and the adenoma was resected. Transsphenoidal surgery took

TABLE 1 | Initial laboratory results of the patient.

Test	Result	Unit	Normal range
Complete blood count (CBC)			
WBC	9.94	$10^3/\mu L$	3.5–12
Lymphocytes	4.48 (H)	$10^3/\mu L$	—
RBC	5.19	$10^6/\mu L$	4.5–6
Hemoglobin	14.2	g/dL	13–18
Hematocrit	43	%	39–54
Platelets	383	$10^3/\mu L$	145–450
PDW	8.9 (L)	fL	9–17
MPV	8.5 (L)	fL	9–13
Comprehensive metabolic panel (CMP)			
Fasting blood sugar	90	mg/dL	70–115
Hb A1 C	5.5	%	4.8–5.9
Creatinine	0.49 (L)	mg/dL	0.7–1.4
Sodium	138	mEq/L	135–145
Potassium	4.2	mEq/L	3.5–5
Calcium	10.3	mEq/dL	8.8–11 (children)
Phosphorus	4.9	mEq/dL	4–6.5 (children)
ESR 1st hour	10	mm	0–20
Hormone analysis			
T_4	10.3	μg/dL	5.1–14.1
Vitamin D-3	5.6 (L)	ng/mL	30–100
TSH	0.75	uIU/mL	0.54–5.5 (children)
Prolactin	14.6	ng/mL	
Cortisol 8 a.m.	677.1 (H)	ng/mL	171–536
ACTH	75.3 (H)	pg/mL	7.2–63.3
Testosterone	< 0.20	ng/mL	0.03–0.32
17-OH Progesterone	0.66	ng/mL	0.31–1.68
Ferritin	27.1	ng/mL	13–150
Growth hormone basal	0.37	ng/mL	Up to 8.0
Insulin	24.1	μU/mL	2.6–29.1
Urine analysis			
Specific gravity	1.015	—	1.005–1.030
pH	8	—	4.6–8

Abbreviations: ACTH, adrenocorticotropic hormone; ESR, erythrocyte segmentation rate; H, high; L, low; MPV, mean platelet volume; PDW, platelet distribution width; RBC, red blood cell; TSH, thyroid stimulating hormone; WBC, white blood cell.

TABLE 2 | The follow-up laboratory test with suspicion of Cushing's syndrome.

Test	Result	Unit	Normal range
Urine 24 h-cortisol	400 (H)	mg/24 h	19.3–317.5
Serum cortisol 8 a.m.	37.1 (H)	mg/dL	4.3–22.4
ACTH	95 (H)	pg/mL	7.1–56.3

Abbreviations: ACTH, adrenocorticotropic hormone; H, high; L, low.

TABLE 3 | Overnight and low-dose dexamethasone suppression test.

Test	Result	Unit	Normal range
Overnight dexamethasone suppression test			
ACTH	115 (H)	pg/mL	7.1–56.3
Cortisol 8 a.m.	119 (H)	ug/dL	4.3–22.4
Low dose dexamethasone suppression test			
ACTH	57 (H)	pg/mL	7.1–56.3
Cortisol 8 a.m.	28 (H)	ug/dL	4.3–22.4

Abbreviations: ACTH, adrenocorticotropic hormone; H, high; L, low.

almost 3 h, and the macroadenoma tumor was resected from the posterior portion of the anterior thyroid through the air sinuses. The immunohistochemistry (IHC) staining revealed that the tumor cells were positive for ACTH but negative for prolactin, growth hormone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), TSH, and P53. Only 2% of the cells were positive for Ki67, which is insignificant.

2.3 | Follow-Up

The day after the TSS, ACTH was 9.9 pg/mL (normal range < 46 pg/mL), cortisol at 8 a.m. was 1.9 μg/dL (normal range 3.7–19.4 μg/dL); the patient was treated with the physiologic dose of hydrocortisone (hydrocortisone 2 mg per kg every 4 h, intravenously). The patient responded to this treatment, and the ACTH and cortisol levels rose to normal within a week. The patient's height and weight were 105 cm and 27.8 kg, respectively, at discharge. He experienced no post-surgical complications such as polyuria and polydipsia. Post-surgical urine specific gravity was 1.024, which was within the normal range. After 6 months of surgery, his height was 109.5 cm, his weight decreased to 25 kg, and his BMI was 21.8 kg/m^2. The moon face, buffalo hump, and central obesity disappeared. All biochemical results were in the normal range, including ACTH, TSH, free thyroxine (T4), prolactin, insulin-like growth factor 1 (IGF1), and urinary-specific gravity.

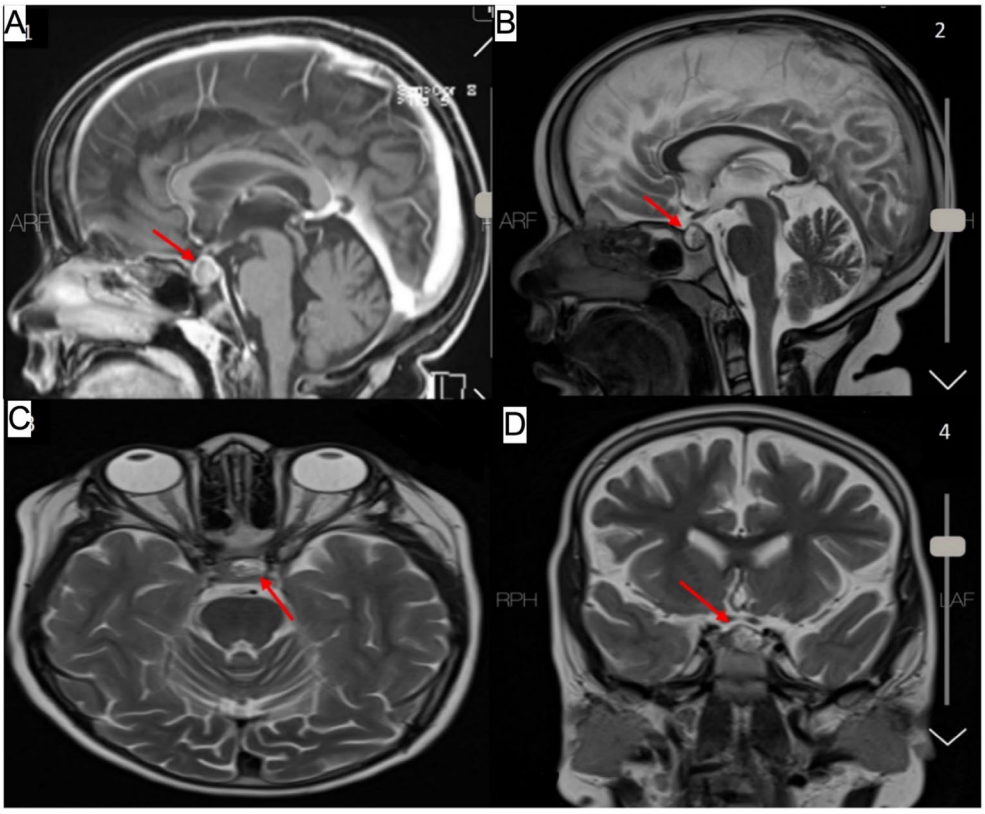

FIGURE 1 | These MRI images with (Figure A) and without (images B, C, and D) contrast (Gadolinium) confirm the diagnosis of pituitary adenoma. The well-defined lesion in the anterior pituitary gland is pointed to with a red arrow in all images. There was no compression on the optic chiasm, according to the MRI images. Image one: T1 in the sagittal plane; Image two: T2 in the sagittal plane; Image three: T2 in the axial plane; and Image four: T2 in the coronal plane.

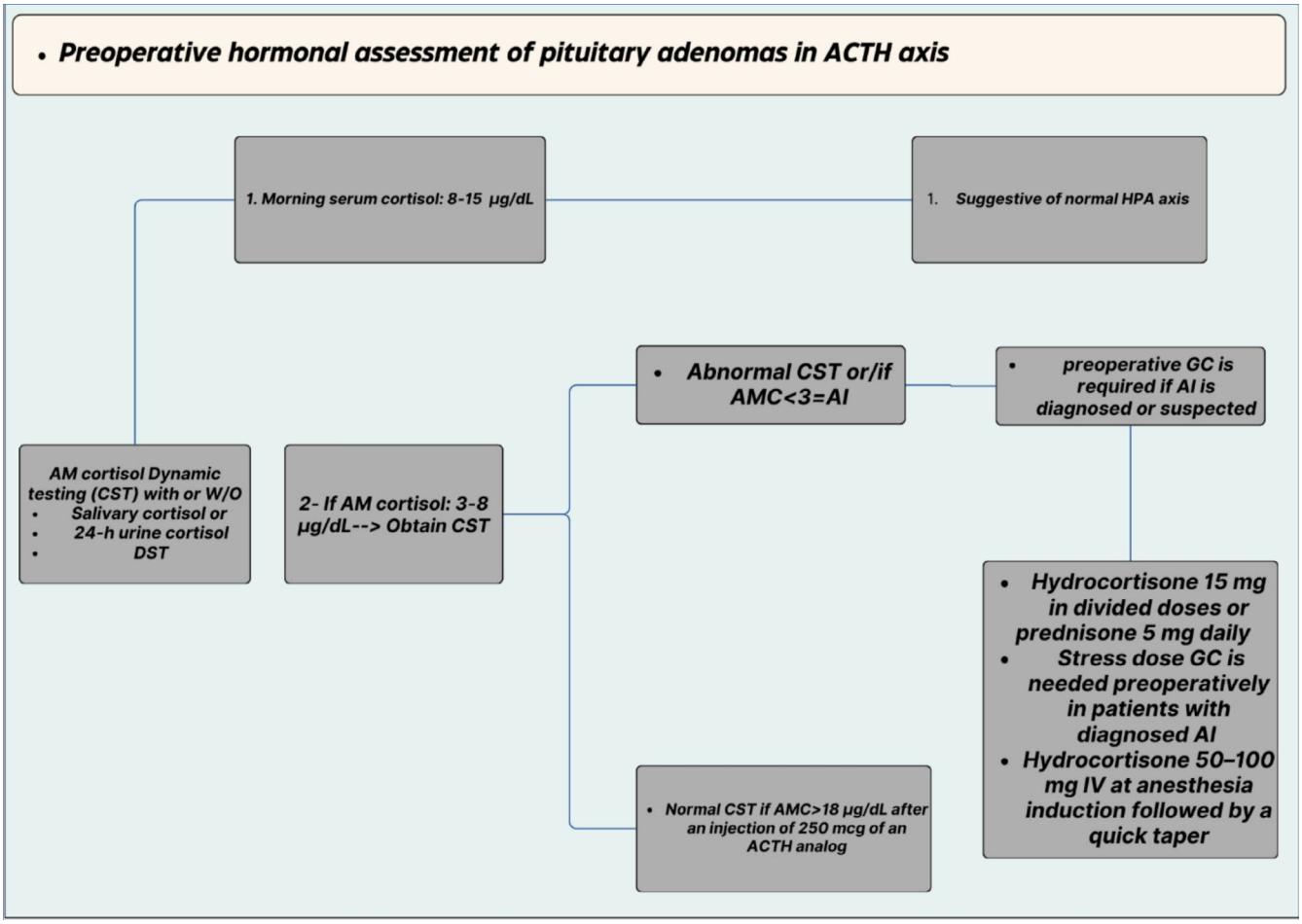

FIGURE 2 | Before surgery, ACTH-secreting pituitary adenomas should be evaluated, and in specific cases, preoperative measures are required. Abbreviations: ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency; AMC, after stimulation morning cortisol; CST, cortisol stimulation test; DST, dexamethasone suppression test; GC, glucocorticoid; HPA, hypothalamic–pituitary–adrenal; IV, intravenous.

3 | Discussion

In the pediatric population, secreting pituitary adenomas are more common than non-secreting pituitary adenomas as they grow slowly and are unlikely to cause symptoms in childhood. Prolactin-secreting tumors, among hormone-secreting adenomas, are the most common pediatric tumors [6, 7]. Among all pituitary adenoma incidences, 3%–9% happen in pediatric patients. ACTH-secreting pituitary adenoma is a rare tumor in the pediatric population that causes Cushing's disease. While ACTH-secreting pituitary adenomas are more common in girls, with a 3:1 ratio in the general population, their frequency is similar in different sexes in the pubertal age group. However, they are more common in male patients in the prepubertal population, and following puberty, they are more common in female patients [8, 9]. The median age of Cushing's disease based on 182 cases is 14.1, but the age of our patient is 6 years old [10]. The most common symptom in patients with Cushing's disease is a Cushingoid appearance, characterized by symptoms such as obesity, moon face, and striae. Although our patient exhibited the first two symptoms, he showed no striae. Other symptoms, including muscle weakness, sleep disorders, mood changes, and growth failure, may also be present [9]. Cushing's disease diagnosis might be challenging due to other possible differential diagnoses.

In this case report, the size of the pituitary adenoma was 12 × 8 mm, and it did not have any mass effects on the surrounding tissues. Prior studies also reported that the most common pituitary adenoma in the pediatric population is a microadenoma with a 1–40 mm range [11, 12]. Many pituitary adenoma cases are due to genetic conditions such as multiple endocrine neoplasia type 1 (MEN1) or McCune–Albright syndrome. Still, our patient had no family history suggesting those conditions.

The most common presenting signs of pituitary adenomas are hormonal complications. The neurological symptoms appear later in the disease as the tumor grows [2]. Cushing's disease is present with ACTH elevation and hypercortisolism. An ACTH above the normal range with hypercortisolism symptoms is suggestive of ACTH-dependent hypercortisolism, as our patient presented. One of the differential diagnoses of Cushing's disease is ectopic ACTH secretion, which should be ruled out by various tests such as dexamethasone suppression tests [13]. According to Storr et al. [14], the majority of pediatric patients with Cushing's disease failed to suppress serum cortisol after the low dose of the dexamethasone suppression test, just as our patient did. In our patient's case, the level of ACTH after the overnight dexamethasone suppression test and the low-dose dexamethasone suppression test was above the normal but not significantly high, which

was not the case with ectopic ACTH-secreting tumors. With a susceptibility to ACTH-secreting pituitary adenoma and symptoms like the patient's occasional headaches, MRI is considered a diagnostic tool, and it confirmed the pituitary adenoma in our case [14, 15].

The other factor that is considerable about pituitary adenomas is their location; it requires a complicated surgical approach that requires highly skilled neurosurgeons to perform the surgery because it could have severe complications in a very young patient like ours. Due to possible severe complications of hypopituitarism after the surgery, such as infertility, diabetes insipidus (DI), and growth restriction, the case was consulted with highly expert-trained pediatric neurosurgeons, and the TSS has been scheduled under optimal operation conditions. TSS is the most common type used for resecting pituitary adenomas, and prior studies have reported the benefits of this surgery over other surgical options [16]. TSS resection is the first-line surgical approach for patients with Cushing's disease, with a success rate above 90%; however, the success rate can decrease to 60% in repeated surgery due to recurrence [9, 17]. After surgery, cortisol production may temporarily decrease due to the inhibition of the adrenal axis. In this case, glucocorticoids should be prescribed [9]. No other complications were observed after the TSS in the presented patient in this study. According to prior literature reviews, the other concerning fact is the high recurrence rate of adenoma (54%) after the first surgery on these tumors. Managing pediatric patients with advanced, recurrent tumors is more challenging than managing adult patients [8, 9, 16]. Therefore, more frequent follow-ups by primary care physicians were advised to the patient's parent.

Preoperative and nonsurgical management, which can reduce the risk of surgery, should be considered in the management of ACTH-secreting pituitary adenoma. The schematic figure below (Figure 2) mentions one of the most recently recommended approaches by Shafiq et al. (2024) [18]. The take-home message of this study can be summarized as follows: when patients are presented with Cushing's disease without usual background risk factors, a careful examination should be done according to the guidelines (Endocrine Society Clinical Practice Guideline) [19]. These assessments aim to confirm Cushing's disease and verify the ACTH-secreting pituitary adenoma with an MRI. As surgery is the first-line option, it should be consulted and done with a well-trained neurosurgeon due to the complexity of the case, the possibility of recurrence, and hypopituitarism, such as infertility, DI, and growth restriction.

Author Contributions

Shadi Niliyeh: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision. **Fatemeh Sayarifard:** conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision. **Ali Moradi:** conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision. **Aria Setoodeh:** conceptualization, project administration, software, supervision, validation, visualization, writing – original draft, writing – review and editing. **Pouya Ebrahimi:** conceptualization, project administration, supervision, visualization, writing – original draft, writing – review and editing.

Acknowledgments

We express our gratitude to the parents of the patient, who provided valuable data for the research discussed in the publication.

Consent

Written informed consent was obtained from the patient's parents to publish this report in accordance with the journal's patient consent policy.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available on request due to privacy/ethical restrictions.

References

1. B. M. Arafah, D. Prunty, J. Ybarra, M. L. Hlavin, and W. R. Selman, "The Dominant Role of Increased Intrasellar Pressure in the Pathogenesis of Hypopituitarism, Hyperprolactinemia, and Headaches in Patients With Pituitary Adenomas," *Journal of Clinical Endocrinology and Metabolism* 85, no. 5 (2000): 1789–1793.

2. M. G. Lake, L. S. Krook, and S. V. Cruz, "Pituitary Adenomas: An Overview," *American Family Physician* 88, no. 5 (2013): 319–327.

3. A. F. Daly, M. A. Tichomirowa, and A. Beckers, "The Epidemiology and Genetics of Pituitary Adenomas," *Best Practice & Research. Clinical Endocrinology & Metabolism* 23, no. 5 (2009): 543–554.

4. J. Chen, R. E. Schmidt, and S. Dahiya, "Pituitary Adenoma in Pediatric and Adolescent Populations," *Journal of Neuropathology and Experimental Neurology* 78, no. 7 (2019): 626–632.

5. N. Zhang, P. Zhou, Y. Meng, F. Ye, and S. Jiang, "A Retrospective Review of 34 Cases of Pediatric Pituitary Adenoma," *Child's Nervous System* 33, no. 11 (2017): 1961–1967.

6. M. D. Partington, D. H. Davis, E. R. Laws, and B. W. Scheithauer, "Pituitary Adenomas in Childhood and Adolescence: Results of Transsphenoidal Surgery," *Journal of Neurosurgery* 80, no. 2 (1994): 209–216.

7. L. A. Kane, M. C. Leinung, B. W. Scheithauer, et al., "Pituitary Adenomas in Childhood and Adolescence," *Journal of Clinical Endocrinology & Metabolism* 79, no. 4 (1994): 1135–1140.

8. A. Perry, C. S. Graffeo, C. Marcellino, B. E. Pollock, N. M. Wetjen, and F. B. Meyer, "Pediatric Pituitary Adenoma: Case Series, Review of the Literature, and a Skull Base Treatment Paradigm," *Journal of Neurological Surgery. Part B, Skull Base* 79, no. 1 (2018): 91–114.

9. R. Pomahacova, P. Paterova, E. Nykodymova, J. Sykora, and M. Krsek, "Pediatric Cushing's Disease: Case Reports and Retrospective Review," *Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czech Republic* 168, no. 1 (2024): 85–91.

10. M. O. Savage and H. L. Storr, "Pediatric Cushing's Disease: Management Issues," *Indian Journal of Endocrinology and Metabolism* 16, no. Suppl 2 (2012): S171–S175.

11. P. Nomikos, C. Ladar, R. Fahlbusch, and M. Buchfelder, "Impact of Primary Surgery on Pituitary Function in Patients With Non-Functioning Pituitary Adenomas—A Study on 721 Patients," *Acta Neurochirurgica* 146, no. 1 (2004): 27–35.

12. N. Fatemi, J. R. Dusick, C. Mattozo, et al., "Pituitary Hormonal Loss and Recovery After Transsphenoidal Adenoma Removal," *Neurosurgery* 63, no. 4 (2008): 709–718.

13. G. Dickstein, C. R. DeBold, D. Gaitan, et al., "Plasma Corticotropin and Cortisol Responses to Ovine Corticotropin-Releasing Hormone (CRH), Arginine Vasopressin (AVP), CRH Plus AVP, and CRH Plus

Metyrapone in Patients With Cushing's Disease," *Journal of Clinical Endocrinology and Metabolism* 81, no. 8 (1996): 2934–2941, https://doi.org/10.1210/jcem.81.8.8768855.

14. H. L. Storr, K. I. Alexandraki, L. Martin, et al., "Comparisons in the Epidemiology, Diagnostic Features and Cure Rate by Transsphenoidal Surgery Between Paediatric and Adult-Onset Cushing's Disease," *European Journal of Endocrinology* 164, no. 5 (2011): 667–674.

15. G. A. Kaltsas, M. G. Giannulis, J. D. Newell-Price, et al., "A Critical Analysis of the Value of Simultaneous Inferior Petrosal Sinus Sampling in Cushing's Disease and the Occult Ectopic Adrenocorticotropin Syndrome," *Journal of Clinical Endocrinology and Metabolism* 84, no. 2 (1999): 487–492.

16. Y. Esquenazi, W. I. Essayed, H. Singh, et al., "Endoscopic Endonasal Versus Microscopic Transsphenoidal Surgery for Recurrent and/or Residual Pituitary Adenomas," *World Neurosurgery* 101 (2017): 186–195.

17. T. Woodcock, P. Barker, S. Daniel, et al., "Guidelines for the Management of Glucocorticoids During the Peri-Operative Period for Patients With Adrenal Insufficiency," *Anaesthesia* 75, no. 5 (2020): 654–663.

18. I. Shafiq, Z. R. Williams, and G. E. Vates, "Advancement in Perioperative Management of Pituitary Adenomas-Current Concepts and Best Practices," *Journal of Neuroendocrinology* 36 (2024): e13427.

19. L. K. Nieman, B. M. K. Biller, J. W. Findling, et al., "The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline," *Journal of Clinical Endocrinology & Metabolism* 93, no. 5 (2008): 1526–1540.