Endotext

# CUSHING SYNDROME/DISEASE IN CHILDREN AND ADOLESCENTS

**Christina Tatsi, MD, MHSc, PhD,** Assistant Clinical Investigator, Unit on Hypothalamic and Pituitary Disorders, *Eunice Kennedy Shriver* National Institute of Child Health, and Human Development, National Institutes of Health, Bethesda, MD, 20814, USA. christina.tatsi3@nih.gov

**Received March 13, 2024**

## ABSTRACT

Endogenous Cushing syndrome (CS) is a rare pediatric endocrine condition commonly caused by pituitary corticotroph tumors or less often by adrenal or ectopic sources. The typical presentation of the child with CS includes weight gain with height deceleration, characteristic skin findings, and hormonal and biochemical findings indicative of excessive glucocorticoid production. The diagnostic evaluation of the patient with suspected hypercortisolemia initially involves the confirmation of cortisol excess in blood and/or urine, and then the identification of source. The first line of management usually requires surgical treatment of a pituitary or adrenal lesion. In persistent or recurrent disease, re-operation, medical treatment, or radiation should be considered.

## INTRODUCTION

Cushing syndrome (CS) describes the exposure of the body to supraphysiologic levels of glucocorticoids. Although exogenous (iatrogenic) CS is common, endogenous pediatric CS, is a rare pediatric endocrine condition. Population studies of the incidence of the disease have shown that endogenous CS occurs in about 3-50 cases per million people per year, depending on the population studied; pediatric patients in these studies represent 6-7% of all cases (1-3).

## ETIOLOGY

Endogenous CS can be classified as ACTH-dependent (pituitary or ectopic) or ACTH-independent CS (adrenal-related, Table 1) (4). The etiology of pediatric CS differs based on the age group of the patient (5). In patients younger than 5 years of age, ACTH-independent CS is more common compared to older children and adolescents who usually present with ACTH-dependent CS. Ectopic CS (ECS) is rare at any age group (5).

| Table 1. Causes of Cushing Syndrome | | |
|---|---|---|
| **Type** | **Source** | **Mechanism** |
| **Exogenous** | | |
| | Iatrogenic | Exogenous administration of supraphysiologic doses of glucocorticoids or ACTH |
| **Endogenous** | | |
| **ACTH-dependent** | Pituitary | Corticotroph pituitary neuroendocrine tumor |
| | | Pituitary blastoma |
| | Ectopic | Neuroendocrine tumors secreting ACTH and/or CRH |
| **ACTH-independent** | Unilateral adrenal (except in metastatic disease) | Cortisol-secreting adrenocortical adenomas and carcinomas |
| | Bilateral adrenals | Bilateral micronodular adrenocortical disease<br>Primary pigmented nodular adrenocortical disease (PPNAD), isolated or in the context of Carney complex<br>Isolated micronodular adrenocortical disease (iMAD) |
| | | Bilateral macronodular adrenocortical disease |

**ACTH-Dependent Cushing Syndrome**

ACTH-dependent CS is most commonly due to a corticotroph pituitary neuroendocrine tumor (PitNET, also called pituitary adenoma or Cushing disease, (CD). These are monoclonal lesions that continue to express some of the characteristics of the normal corticotroph cell which can be useful in the diagnostic evaluation of patients (6, 7). Corticotroph-secreting PitNETs are usually microadenomas with median diameter of 5mm and do not often show signs of invasion to the cavernous sinus or other parasellar structures (8). Rare cases of aggressive PitNETs have been reported in the pediatric population with either resistance to treatment or distant metastasis (metastatic PitNETs) (9). These are associated with specific histologic subtypes, such as Crooke cell adenomas (9).

Infantile onset of ACTH-dependent CS with a pituitary lesion is often due to a pituitary blastoma. In 2014 de Kock *et al*, collected tissues from several infants who had been diagnosed with very young onset CD and reported that the tumors were consistent with pituitary blastomas as they had histologic findings of undifferentiated epithelium Rathke-like cells, mixed with hormone producing cells (10). They were able to identify germline and/or somatic *DICER1* gene defects in these patients, suggesting that pituitary blastoma is a rare but almost pathognomonic presentation of DICER1 syndrome (10).

ECS is due to neuroendocrine tumors secreting ACTH and/or CRH outside the hypothalamic-pituitary axis. In older children and adolescents, the most common source of ECS are bronchial carcinoids, thymic carcinoids, and gastro-entero-pancreatic NETs (11-13). By contrast, in children younger than 5-10 years of age, ECS often presents in the context of pediatric specific tumors such as Wilm's tumors, neuroblastomas, and others (13, 14).

**ACTH-Independent Cushing Syndrome**

ACTH-independent CS is commonly caused by unilateral adrenocortical tumors, cortisol-producing adenomas or carcinomas (5). Cortisol-producing adenomas are benign lesions with isolated cortisol

secretion, while adrenocortical carcinomas are aggressive tumors and may commonly co-secrete cortisol and androgens in up to 80% of all cases (15, 16).

Bilateral adrenocortical disorders account for <2% of all cases of CS but some subtypes may be more prevalent in children compared to adults given their association with germline genetic defects (17). Micronodular adrenocortical disease is the most common type of bilateral adrenocortical disorder in pediatric patients. This category may be further divided in primary pigmented micronodular adrenocortical disease (PPNAD) where the adrenals present with multiple dark brown pigmented micronodules (due to lipofuscin deposition with most with diameter of <1cm) with internodular cortical atrophy, or the absence of these findings referred to as isolated micronodular adrenocortical disease (i-MAD) (18). PPNAD may be identified in the context of Carney complex (CNC) and less often as isolated PPNAD (19). Bilateral macronodular adrenocortical disease presenting with bilateral macronodules (most with diameter of ≥1cm) is rare in the pediatric population.

## GENETICS

Genetic causes are found in less than half of the patients with pediatric CD and more commonly in adrenal-related CS. For patients presenting with pediatric onset CS, it is recommended to obtain genetic testing directed to the source of hypercortisolemia, i.e. adrenal vs. pituitary causes. Although the yield in CD may be low, in cases of pituitary blastomas or bilateral micronodular disease genetic testing has higher chance of identifying the genetic cause and lead to screening for other related manifestations that may be important, such as cardiac myxomas in patients with CNC.

### ACTH-Dependent Cushing Syndrome

Germline mutations are identified in less than 10% of patients with pediatric CD (8). Of the most common causes are *MEN1* (causing multiple endocrine neoplasia type 1 syndrome, MEN1), *CDKN1B* (causing MEN4), and *CABLES1* gene defects (20). Genes associated with familiar isolated pituitary adenoma (FIPA) syndrome, such as *AIP*, *SDHx*, and *MAX*, or syndromes associated with pituitary tumors amongst other manifestations, such as CNC due to *PRKAR1A* gene defects, do not commonly cause corticotropinomas and have only been reported in few case reports (21).

As mentioned above, young children (<2 years old) presenting with pituitary blastomas should be screened for *DICER1* gene defects (10). DICER1 codes for an endoribonuclease that processes miRNAs (22). Patients with DICER1 or pleuropulmonary syndrome present with multiple tumors in lungs, kidneys, multinodular goiter, and other manifestations. Pituitary blastomas are present in less than 10% of all patients and always within the first years of life (23).

Somatic mutations are more likely to be identified in corticotropinomas. *USP8* mutations in the 14-3-3 binding motif hotspot region of the gene have been reported as the cause of 40-60% of adults with CD (24, 25). Pediatric data suggest that *USP8* mutations are less common and identified in up to 30% of cases (26). USP8 is a deubiquitinase involved in recycling of the epidermal growth factor receptor (EGFR) and mutations in the hotspot region led to increased catalytic activity, activation of the EGF pathway, and increased *POMC* expression. In children, *USP8* mutant tumors presented with larger size and higher risk for persistent disease after surgery or recurrence after initial remission (26). Data in adult patients did not confirm this finding, and the prognostic value of identifying a *USP8* mutation is still unclear (27). Other somatic mutations identified in corticotropinomas include *USP48*, *TP53*, and *BRAF*, but the incidence in

pediatric patients is unknown (28). Finally, in a subset of patients with pediatric corticotropinomas large genomic chromosomal deletions/gains are identified and are associated with larger tumor and higher risk of invasion of the cavernous sinus (29).

ECS may present in various neuroendocrine tumors and the genetic background is associated with the primary tumor. MEN1, MEN2 (*RET* gene mutations), and some gene fusions have been described according to the tissue involved in ectopic ACTH secretion (30, 31).

**ACTH-Independent Cushing Syndrome**

Pediatric cortisol producing adrenocortical carcinomas may present in the context of *TP53* mutations (32). In the Brazilian South and Southeast population, high prevalence of a germline founder *TP53* mutation (p.R337H) is associated with high incidence of pediatric adrenocortical carcinomas (33, 34). Germline *TP53* mutations may also present as Li-Fraumeni syndrome where patients have high risk for breast, central nervous system, bone, and other tumors (35). Cortisol-producing adrenocortical adenomas may be associated with gene defects leading to activation of the cyclic AMP (cAMP) protein kinase A (PKA) pathway, such as somatic mutations in *PRKACA, PRKAR1A*, and *PRKACB* genes (36, 37). Finally, somatic gene defects in the Wnt signaling pathway have also been identified in adrenocortical tumors (38).

ACTH-independent CS due to PPNAD presents commonly in the context of CNC (39). CNC is an autosomal dominant multiple neoplasia syndrome caused by inactivating mutations of the gene *PRKAR1A*, coding for the regulatory subunit 1 alpha of PKA, or less often linked to a second locus at chromosome 2p16 (40-42). Inactivating mutations in *PRKAR1A* lead to constitutive activation of PKA and downstream pathways (18). Patients with CNC present with several manifestations including PPNAD, pituitary abnormalities most often presenting as growth hormone dysregulation or acromegaly, thyroid nodules or carcinomas, testicular tumors, cardiac and skin myxomas, characteristic skin lesions, breast myxomatosis or adenomas, osteo-chondro-myxomas and psammomatous melanotic schwannomas (40). PPNAD in CNC is often diagnosed in the third decade of life but patients as young as in the first decade of life have been reported (43). Additional information about CNC can be found in the chapter entitled “Carney Complex” of Endotext (40).

Additional genetic defects associated with bilateral adrenocortical disease include *PRKACA* genomic gains, *PDE11A*, and *PDE8A* gene defects identified in patients with macronodular adrenocortical disease or isolated micronodular disease (44-46). *PRKACA* codes for the catalytic subunit of PKA, and chromosomal gains lead to increased PKA signaling (47). *PDE11A* and *PDE8A* codes for phosphor-diesterases that catalyze and decrease cAMP levels. Inactivating mutations in these genes lead to increased circulation of cAMP and increased PKA activity (44, 48). Macronodular adrenocortical disease due to *ARMC5* gene defects often seen in adults is rare in the pediatric population (49).

Neonatal ACTH-independent CS may be seen in the context of McCune-Albright syndrome (MAS) (50). In these cases, CS presents within the first year of life and may have detrimental and rapidly developing symptoms which may even lead to death. However, if managed medically, neonatal CS in MAS may resolve on its own (51). Rare cases of neonatal onset adrenocortical disease have also been reported in the context of Beckwith-Wiedemann syndrome (52, 53).

**PRESENTATION**

The presentation of pediatric CS has similarities and differences from that in adults (Table 2).

| Table 2. Presenting Findings in Pediatric Patients with Cushing Syndrome | |
|---|---|
| **Clinical findings** | |
| Anthropometric | Height deceleration |
| | Weight gain |
| Cardiovascular | Hypertension |
| Musculoskeletal | Fractures |
| | Proximal muscle weakness |
| Skin | Striae |
| | Facial Plethora |
| | Easy bruising |
| | Acne |
| | Hirsutism |
| | Acanthosis nigricans |
| | Abnormal fat deposition |
| Neuropsychiatric | Behavioral changes (compulsive behavior, overachievement tendency, irritability) |
| | Psychiatric disorders (depression, anxiety) |
| | Changes in cognitive function |
| | Sleep disturbance (difficulty falling asleep) |
| | Memory problems |
| Reproductive system | Delayed puberty |
| | Irregular menses |
| Immunologic | Increased risk for infections |
| **Laboratory and imaging findings** | |
| Complete blood count | Elevated total white blood cell, neutrophil and monocyte counts |
| | Decreased lymphocyte and eosinophil count |
| | Elevated neutrophil-to-lymphocyte ratio |
| Biochemistry | Hypokalemia |
| | Hypercalciuria |
| | Elevated ALT |
| | Hyperlipidemia |
| | Hyperglycemia with elevated insulin levels |
| Coagulation factors | Increased coagulation factors |
| | Decreased aPTT |
| Echocardiogram | Cardiac hypertrophy |
| DXA | Decreased bone mineral density |

The hallmark of pediatric CS is weight gain with concomitant height deceleration (Figure 1) (54). This finding can help discriminate patients with CS from with simple obesity who often have preserved height percentile (55). Fat deposition in pediatric patients may not be as prominently centripetal as noted in adults, and may present often as generalized obesity similar to other causes (56). Although height deceleration is seen in most cases of growing children, patients may not be short at presentation, may have completed growth by the time hypercortisolemia occurred, or may be exposed to episodic

hypercortisolemia which may have more limited effect on their height (5, 8, 57). Bone age is often within the expected range for the chronologic age or advanced in pediatric patients with endogenous CS, and is correlated with the levels of adrenal androgens which are often increased in ACTH-dependent CS (58).

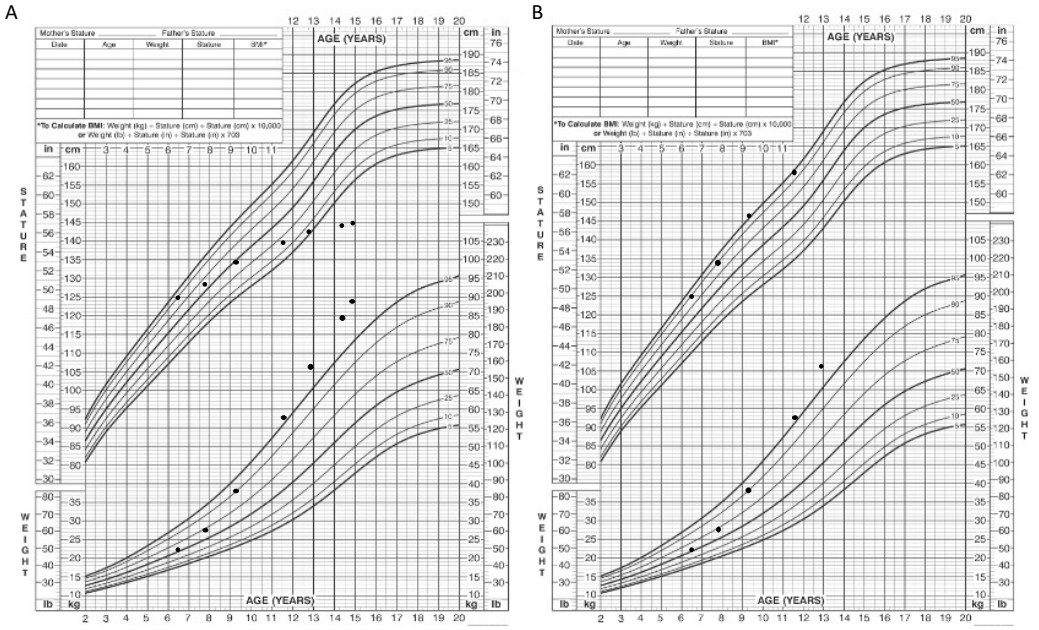


**Figure 1. Typical growth chart of a pediatric patient with Cushing syndrome (A) compared to a child with obesity (B).**

Dermatologic findings present in CS include striae (which are present in 60-80% of patients and may not have the characteristic appearance of deep purple color and thickness as in adults), facial plethora, acne (more common in ACTH-dependent CS possibly due to stimulation of adrenal zona reticularis by ACTH), hirsutism in women, hypertrichosis, acanthosis nigricans, and easy bruising (8, 56, 59).

Patients with CS often present with delayed puberty in males and females and/or irregular menses and secondary amenorrhea in females (8).

As in patients with iatrogenic CS, pediatric patients with endogenous CS present with decreased bone mineral density, with lower scores in the spinal measurements (60-62). Proximal muscle weakness although reported is less frequent than adult patients (54).

Pediatric patients with endogenous CS, especially younger in age, often present with behavioral and neurocognitive changes. They may report behavioral changes including compulsive behaviors with overachievement goals, described as excellent students, along with increased anxiety and irritability (63). They may also report mood changes, depressed mood, sleep problems, and memory issues similar to adults. Headaches are common in pediatric patients and can be noted in up to 80% of them (8).

Hypercortisolemia and its related obesity lead to metabolic syndrome (64). Patients often present with insulin resistance and up to 30% of patients may have impaired glucose metabolism (56). Hyperlipidemia and elevated ALT as a surrogate marker of metabolic associated fatty liver disease (MAFLD) are also present in almost half of the patients (8, 56). Hypertension is present in almost 50% of patients with endogenous CS and cases of posterior reversible encephalopathy syndrome (PRES) due to

hypertensive emergency have been reported as the initial manifestation of CS in pediatric patients (8, 65).

Similar to adults, pediatric patients with CS present with a hypercoagulable state associated with abnormal levels of procoagulants, antifibrinolytics, and anticoagulant factors, such as factor VIII, antithrombin III, protein C and S, and prolonged partial thromboplastin time (PTT) (66). Although in adult patients with CS the risk of venous thromboembolism is more studied, the exact incidence, risk, and thromboprophylaxis protocols in children are not as well delineated and depend on clinical judgement (67).

Additional findings in pediatric CS include characteristic abnormalities in CBC due to glucocorticoids effects including increased WBC count, neutrophil count, low normal lymphocyte count, and increased neutrophil-to-lymphocyte ratio (NLR) (68). Although immunosuppression may lead to severe infections in patients with significantly elevated cortisol levels, in most pediatric cases infections are limited to less clinically significant areas such as skin infections etc. (69). However, in very young patients, especially in neonatal CS, or patients with severe hypercortisolemia, such as in ECS, opportunistic infections may lead to significant morbidity and even death and prophylaxis should be initiated (14, 70).

Electrolyte abnormalities seen in endogenous CS include hypokalemia, uncommon overall but seen more frequently in ECS, and hypercalciuria which may lead to nephrolithiasis (8, 71).

Patients with hypercortisolemia also present with other hormonal defects including abnormal thyroid function test with a pattern of central hypothyroidism, abnormal GH secretion with IGF-1 levels usually preserved within the reference range, and suppressed gonadotropins (72-75). Tumor stalk compression effects may lead to hyperprolactinemia, although this is uncommon due to the small size of most corticotropinomas. Androgen levels are commonly elevated in ACTH-dependent CS due to adrenal zona reticularis stimulation from ACTH, or in adrenocortical carcinomas where co-secretion of cortisol and DHEAS may be seen.

## DIAGNOSIS

The diagnostic evaluation of pediatric CS follows the guidelines of the endocrine and pituitary society adjusted for the pediatric population (7, 76, 77). Screening for hypercortisolemia is preferably done with at least two of the following tests: 24-hour urinary free cortisol (UFC, measured on 2-3 days), midnight (or late night) cortisol measured on 2-3 days, and suppression of cortisol to low dose dexamethasone (76). Specific details on these tests can be found in the chapter entitled “Endocrine Testing Protocols: Hypothalamic Pituitary Adrenal Axis” of Endotext (78).

### Confirming the Diagnosis of Cushing Syndrome

The loss of the diurnal rhythm of ACTH/cortisol secretion is the first abnormality noted in patients with CS (79, 80). In clinical practice, salivary cortisol has been used to measure midnight or late night cortisol levels as it is convenient and can be collected at home (78, 81). If this is not available, then serum midnight cortisol is an alternative accurate screening test (77). A serum cortisol level of ≥4.4mcg/dL was able to distinguish almost all pediatric patients with CS with a sensitivity of 99% and a specificity of 100% (7). Serum cortisol needs to be measured from an indwelling catheter that has been placed at least 2 hours prior to sampling. We instruct patients to turn off all screens by 10pm and blood should be collected without awakening the patient (82).

The 24-hour urine collection should be performed on two or three days, to ensure optimal urine collection and account for the known day-to-day variability in urinary cortisol in patients with CS (83, 84). It is generally recommended to collect urine on days of routine physical activities and avoid days when increased stressful activities are expected, like competitive sports games etc. (85). Additionally,

patients are advised to consume normal amount of fluids as excessive fluid intake and urine output may lead to false positive results (86). The urine samples should be measured for urine creatinine to ensure normal kidney function, but we do not routinely correct UFC levels for the urine creatinine level as this may lead to inaccurate results (87).

The low dose or 1mg overnight dexamethasone suppression test is performed similar to adults (78). Dose adjustment has been used in several studies, though no study has been done to specifically investigate the appropriate dose in children with CS. Various protocols recommend the use of 15mcg/kg, 25mcg/kg, or 0.3mg/m2 (max 1mg) once at 11pm for the overnight test or 1200mcg/kg/day (max 2mg/day) divided Q6 hours for two days (88, 89). Measurement of a serum dexamethasone level at the same time as cortisol is important to ensure the desired dexamethasone level has been reached.

If screening labs suggest cortisol excess, it is important to rule out physiologic/non-neoplastic hypercortisolism (previously known as pseudo-Cushing syndrome) (90). If suspicion is high, additional testing should be considered, including dexamethasone-CRH test (if available) or DDAVP stimulation test. If results remain inconsistent, close monitoring with repeat physical examination and labs within 3 months should be offered to monitor clinical and biochemical findings while at the same treating causes that may contribute to activation of the hypothalamic-pituitary-adrenal axis (90).

**Identifying the Source of Hypercortisolemia**

Once endogenous CS is confirmed, the next step is to identify the source of hypercortisolemia. ACTH levels are used to guide next steps. Elevated ACTH levels of >20-29pg/mL suggest ACTH-dependent CS while suppressed ACTH is consistent with ACTH-independent CS (7). Intermediate values may need further evaluation for both ACTH-dependent and ACTH-independent causes, but most often a non-suppressed ACTH level suggests ACTH-dependent CS, except in the case of mild subclinical hypercortisolemia or cyclical CS.

In cases of ACTH-dependent CS, additional biochemical and imaging studies include pituitary MRI (with and without contrast, pituitary protocol), CRH stimulation test (if available), DDAVP stimulation test and/or high dose dexamethasone suppression test. Corticotroph PitNETs are often shown as hypo-enhancing microadenomas in pituitary MRI (Figure 2), but a normal/negative MRI may be seen in up to 30% of patients (91). In cases of normal MRI or biochemical testing inconsistent with pituitary source, bilateral inferior petrosal sinus sampling (BIPSS) is the gold standard in diagnosing or ruling out CD. Non-invasive strategies are described if BIPSS is not feasible and/or not available (92). In our pediatric patients, all patients who showed suppression to high dose dexamethasone administration and stimulation to CRH/DDAVP consistent with a pituitary source, had CD irrespective of imaging findings (8).

For patients suspected to have ECS, further evaluation should include imaging of the neck, chest, abdomen, and pelvis with thin cuts as carcinoids can be small in diameter. Chest imaging is preferably done with CT due to higher accuracy in the lung parenchyma, but some centers use MRI for abdominal/pelvic imaging to reduce radiation. Nuclear imaging, preferably with Ga-68 DOTATATE or, if not available or negative, with 18F-FDG PET, may identify some of these ectopic sources (11, 13, 93). If a lesion found on imaging studies is suspicious but not convincing, one may attempt venous sampling close to the possible lesion for measurement of CRH and/or ACTH and compare the levels to a peripheral source (11). If a gradient is reported then this may further support the diagnosis of ectopic tumor (11). Other markers of potential interest in these cases include chromogranin A and CRH, which may be helpful in the follow-up of patients. Patients with ECS may present with pituitary hyperplasia if CRH is co-secreted, which

should be considered when interpreting the imaging and biochemical results.

When ACTH-independent CS is suspected, imaging of the adrenals is the best next step. Imaging can be preferably with CT since it has good accuracy for lesions <1cm and less artifacts due to motion, but MRI may be an alternative to avoid radiation exposure. Ultrasound however is not accurate in identifying adrenal lesions other than large adrenocortical tumors (14). In ACTH-independent CS, it is important to review the anatomy of both adrenals; noting a unilateral lesion with atrophy of the contralateral adrenal supports the diagnosis of unilateral disease, whereas bilateral symmetrical adrenal enlargement or bilateral normal appearing adrenals suggests bilateral disease (Figure 2). In case of bilateral micronodular adrenocortical disease, adrenal anatomy is often read as normal or sometimes asymmetric appearance of the contour of the adrenals described as “beads on a string” may be apparent (94).

When bilateral adrenocortical disease is suspected, confirmation of the diagnosis prior to proceeding with surgical intervention involves the performance of Liddle’s test (95). The paradoxical increase of urinary free cortisol or 17-hydroxy steroids with increasing doses of dexamethasone is pathognomonic for PPNAD (95).

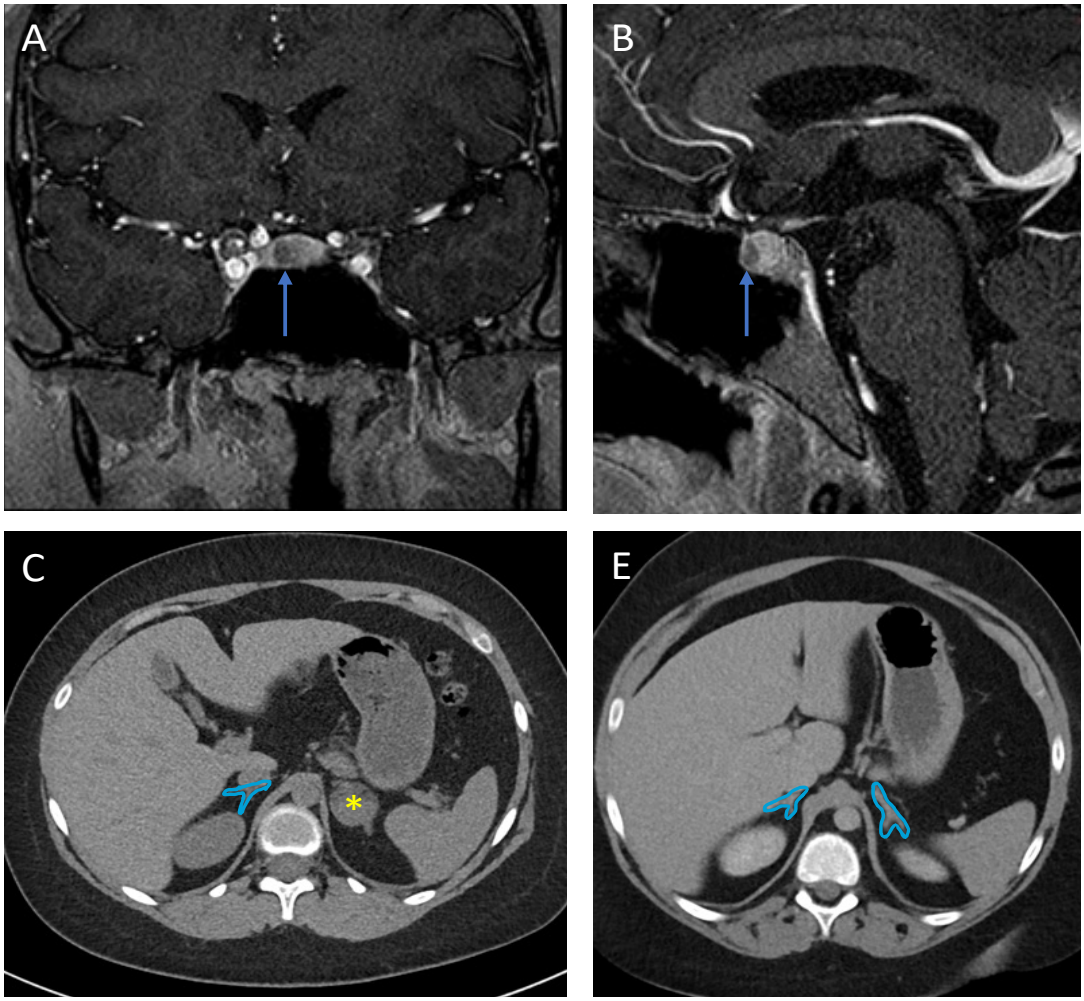


**Figure 2. Typical imaging findings in a patient with Cushing disease (A-B), a cortisol-producing adrenal adenoma (C) and bilateral micronodular adrenocortical disease (E). Postcontrast sagittal (A) and coronal**

**(B) MRI images of the pituitary showing a microadenoma (tip of arrows) as hypoechoic lesion. (C) Axial adrenal CT of a patient with a left adrenal adenoma (yellow asterisk) and atrophic contralateral adrenal (blue outline). (E) Axial adrenal CT of a patient with bilateral micronodular adrenocortical disease showing normal appearing adrenals (blue outline) with bilaterally symmetric thickness of the limbs of the adrenals.**

## TREATMENT

Surgical intervention is the first line of treatment in all types of CS whenever the source is identified. In patients with CD, transsphenoidal resection of the pituitary tumor is the preferred approach. Endoscopic or microscopic approaches have been attempted. A recent meta-analysis has not showed significant differences in the remission rate between the two approaches overall, but endoscopic approach may be preferrable in macroadenomas (96, 97). In very young patients, pneumatization of the sphenoid sinus may be incomplete and the surgical approach more be more difficult but transsphenoidal access is still possible (98). In rare cases of very young children with pituitary lesions or in giant complex pituitary tumors, the transcranial approach may be considered (99). Remission is defined as postoperative nadir cortisol levels of <2-5mcg/dl and early postoperative hypocortisolemia is a sensitive marker of durable remission (76, 100). In cases of non-remission patients may be managed with immediate reoperation and partial hypophysectomy (101). In the pediatric cohorts the remission rate after surgery ranges from 62 to 98% depending on the cohort and the criteria used (8, 102-104).

In cases of ACTH-independent CS, bilateral or unilateral adrenalectomy is recommended depending on the underlying cause (105). Although unilateral adrenalectomy has been suggested in cases of bilateral macronodular adrenocortical disease, data on unilateral adrenalectomy in micronodular adrenocortical disease are not clear (105).

ECS should primarily be managed with surgical resection.

In cases of persistent CD after surgery, medical therapy or radiation should be considered. At this time, no medical therapy for CS in the pediatric population has been approved by the FDA in the US and all treatments are considered as off-label use, but ketoconazole is approved by the European Medical Association for children >12 years of age. Medical therapies are divided in those directed to adrenal steroidogenesis, to pituitary tumor function, or to peripheral glucocorticoid action. Most commonly, steroidogenesis inhibitors are considered first line as they are more potent and faster acting. Of these, ketoconazole, metyrapone, osilodrostat, levo-ketoconazole and others have been used (106). Radiation therapy could be considered as an alternative second-line treatment but requires medical management and close monitoring until the radiation effect is apparent (107, 108). Finally, bilateral adrenalectomy is reserved for cases of severe CS persistent despite surgical or medical intervention. This is followed by lifelong adrenal insufficiency and patients should be monitored for the risk of Nelson syndrome (109).

## POSTOPERATIVE MANAGEMENT

After successful surgical management, patients experience adrenal insufficiency. In CD the median duration of adrenal insufficiency is almost 12 months (110). Additionally, management of patients after remission of CS should also target symptoms of glucocorticoid withdrawal which may require supraphysiologic doses of glucocorticoids for a period of time and slow tapering to physiologic levels (111).

After recovery of the axis, regular screening for possible recurrence should be offered. Long term recurrence has been reported in 8-20% of pediatric

patients with CD after initial postoperative remission (8). Screening for recurrence should be done preferably as in adults with two midnight or late-night salivary cortisol levels or with overnight dexamethasone suppression test annually (76).

## REFERENCES


1. Broder MS, Neary MP, Chang E, Cherepanov D, Ludlam WH. Incidence of Cushing's syndrome and Cushing's disease in commercially-insured patients <65 years old in the United States. Pituitary 2015, 18(3):283-289.
2. Ragnarsson O, Olsson DS, Chantzichristos D, Papakokkinou E, Dahlqvist P, Segerstedt E, Olsson T, Petersson M, Berinder K, Bensing S, Hoybye C, Eden Engstrom B, Burman P, Bonelli L, Follin C, Petranek D, Erfurth EM, Wahlberg J, Ekman B, Akerman AK, Schwarcz E, Bryngelsson IL, Johannsson G. The incidence of Cushing's disease: a nationwide Swedish study. Pituitary 2019, 22(2):179-186.
3. Holst JM, Horvath-Puho E, Jensen RB, Rix M, Kristensen K, Hertel NT, Dekkers OM, Sorensen HT, Juul A, Jorgensen JOL. Cushing's syndrome in children and adolescents: a Danish nationwide population-based cohort study. Eur J Endocrinol 2017, 176(5):567-574.
4. Tatsi C, Stratakis CA. Pediatric Cushing Syndrome; an Overview. Pediatr Endocrinol Rev 2019, 17(2):100-109.
5. Storr HL, Chan LF, Grossman AB, Savage MO. Paediatric Cushing's syndrome: epidemiology, investigation and therapeutic advances. Trends Endocrinol Metab 2007, 18(4):167-174.
6. Herman V, Fagin J, Gonsky R, Kovacs K, Melmed S. Clonal origin of pituitary adenomas. J Clin Endocrinol Metab 1990, 71(6):1427-1433.
7. Batista DL, Riar J, Keil M, Stratakis CA. Diagnostic tests for children who are referred for the investigation of Cushing syndrome. Pediatrics 2007, 120(3):e575-586.
8. Tatsi C, Kamilaris C, Keil M, Saidkhodjaeva L, Faucz FR, Chittiboina P, Stratakis CA. Paediatric Cushing syndrome: a prospective, multisite, observational cohort study. Lancet Child Adolesc Health 2024, 8(1):51-62.
9. Tatsi C, Stratakis CA. Aggressive pituitary tumors in the young and elderly. Rev Endocr Metab Disord 2020, 21(2):213-223.
10. de Kock L, Sabbaghian N, Plourde F, Srivastava A, Weber E, Bouron-Dal Soglio D, Hamel N, Choi JH, Park SH, Deal CL, Kelsey MM, Dishop MK, Esbenshade A, Kuttesch JF, Jacques TS, Perry A, Leichter H, Maeder P, Brundler MA, Warner J, Neal J, Zacharin M, Korbonits M, Cole T, Traunecker H, McLean TW, Rotondo F, Lepage P, Albrecht S, Horvath E, Kovacs K, Priest JR, Foulkes WD. Pituitary blastoma: a pathognomonic feature of germ-line DICER1 mutations. Acta Neuropathol 2014, 128(1):111-122.
11. Karageorgiadis AS, Papadakis GZ, Biro J, Keil MF, Lyssikatos C, Quezado MM, Merino M, Schrump DS, Kebebew E, Patronas NJ, Hunter MK, Alwazeer MR, Karaviti LP, Balazs AE, Lodish MB, Stratakis CA. Ectopic adrenocorticotropic hormone and corticotropin-releasing hormone co-secreting tumors in children and adolescents causing cushing syndrome: a diagnostic dilemma and how to solve it. J Clin Endocrinol Metab 2015, 100(1):141-148.
12. More J, Young J, Reznik Y, Raverot G, Borson-Chazot F, Rohmer V, Baudin E, Coutant R, Tabarin A, Groupe Francais des Tumeurs E. Ectopic ACTH syndrome in children and adolescents. J Clin Endocrinol Metab 2011, 96(5):1213-1222.
13. Yami Channaiah C, Karlekar M, Sarathi V, Lila AR, Ravindra S, Badhe PV, Malhotra G, Memon SS, Patil VA, Pramesh CS, Bandgar T. Paediatric and adolescent ectopic Cushing's syndrome: systematic review. Eur J Endocrinol 2023, 189(4):S75-S87.
14. Tatsi C, Stratakis CA. Neonatal Cushing Syndrome: A Rare but Potentially Devastating Disease. Clin Perinatol 2018, 45(1):103-118.
15. Ribeiro RC, Pinto EM, Zambetti GP, Rodriguez-Galindo C. The International Pediatric Adrenocortical Tumor Registry initiative: contributions to clinical, biological, and treatment advances in pediatric adrenocortical tumors. Mol Cell Endocrinol 2012, 351(1):37-43.
16. Mete O, Erickson LA, Juhlin CC, de Krijger RR, Sasano H, Volante M, Papotti MG. Overview of the 2022 WHO Classification of Adrenal Cortical Tumors. Endocr Pathol 2022, 33(1):155-196.
17. Kamilaris CDC, Stratakis CA, Hannah-Shmouni F. Molecular Genetic and Genomic Alterations in Cushing's Syndrome and Primary Aldosteronism. Front Endocrinol (Lausanne) 2021, 12:632543.
18. Tirosh A, Valdes N, Stratakis CA. Genetics of micronodular adrenal hyperplasia and Carney complex. Presse Med 2018, 47(7-8 Pt 2):e127-e137.
19. Stratakis CA. Adrenocortical tumors, primary pigmented adrenocortical disease (PPNAD)/Carney complex, and other bilateral hyperplasias: the NIH studies. Horm Metab Res 2007, 39(6):467-473.
20. Makri A, Bonella MB, Keil MF, Hernandez-Ramirez L, Paluch G, Tirosh A, Saldarriaga C, Chittiboina P, Marx SJ, Stratakis CA, Lodish M. Children with MEN1 gene mutations may present first (and at a young age) with Cushing disease. Clin Endocrinol (Oxf) 2018, 89(4):437-443.

21. Tatsi C, Flippo C, Stratakis CA. Cushing syndrome: Old and new genes. Best Pract Res Clin Endocrinol Metab 2020, 34(2):101418.
22. Foulkes WD, Priest JR, Duchaine TF. DICER1: mutations, microRNAs and mechanisms. Nat Rev Cancer 2014, 14(10):662-672.
23. Faure A, Atkinson J, Bouty A, O'Brien M, Levard G, Hutson J, Heloury Y. DICER1 pleuropulmonary blastoma familial tumour predisposition syndrome: What the paediatric urologist needs to know. J Pediatr Urol 2016, 12(1):5-10.
24. Reincke M, Sbiera S, Hayakawa A, Theodoropoulou M, Osswald A, Beuschlein F, Meitinger T, Mizuno-Yamasaki E, Kawaguchi K, Saeki Y, Tanaka K, Wieland T, Graf E, Saeger W, Ronchi CL, Allolio B, Buchfelder M, Strom TM, Fassnacht M, Komada M. Mutations in the deubiquitinase gene USP8 cause Cushing's disease. Nat Genet 2015, 47(1):31-38.
25. Ma ZY, Song ZJ, Chen JH, Wang YF, Li SQ, Zhou LF, Mao Y, Li YM, Hu RG, Zhang ZY, Ye HY, Shen M, Shou XF, Li ZQ, Peng H, Wang QZ, Zhou DZ, Qin XL, Ji J, Zheng J, Chen H, Wang Y, Geng DY, Tang WJ, Fu CW, Shi ZF, Zhang YC, Ye Z, He WQ, Zhang QL, Tang QS, Xie R, Shen JW, Wen ZJ, Zhou J, Wang T, Huang S, Qiu HJ, Qiao ND, Zhang Y, Pan L, Bao WM, Liu YC, Huang CX, Shi YY, Zhao Y. Recurrent gain-of-function USP8 mutations in Cushing's disease. Cell Res 2015, 25(3):306-317.
26. Faucz FR, Tirosh A, Tatsi C, Berthon A, Hernandez-Ramirez LC, Settas N, Angelousi A, Correa R, Papadakis GZ, Chittiboina P, Quezado M, Pankratz N, Lane J, Dimopoulos A, Mills JL, Lodish M, Stratakis CA. Somatic USP8 Gene Mutations Are a Common Cause of Pediatric Cushing Disease. J Clin Endocrinol Metab 2017, 102(8):2836-2843.
27. Albani A, Perez-Rivas LG, Dimopoulou C, Zopp S, Colon-Bolea P, Roeber S, Honegger J, Flitsch J, Rachinger W, Buchfelder M, Stalla GK, Herms J, Reincke M, Theodoropoulou M. The USP8 mutational status may predict long-term remission in patients with Cushing's disease. Clin Endocrinol (Oxf) 2018.
28. Chen J, Jian X, Deng S, Ma Z, Shou X, Shen Y, Zhang Q, Song Z, Li Z, Peng H, Peng C, Chen M, Luo C, Zhao D, Ye Z, Shen M, Zhang Y, Zhou J, Fahira A, Wang Y, Li S, Zhang Z, Ye H, Li Y, Shen J, Chen H, Tang F, Yao Z, Shi Z, Chen C, Xie L, Wang Y, Fu C, Mao Y, Zhou L, Gao D, Yan H, Zhao Y, Huang C, Shi Y. Identification of recurrent USP48 and BRAF mutations in Cushing's disease. Nat Commun 2018, 9(1):3171.
29. Tatsi C, Pankratz N, Lane J, Faucz FR, Hernandez-Ramirez LC, Keil M, Trivellin G, Chittiboina P, Mills JL, Stratakis CA, Lodish MB. Large Genomic Aberrations in Corticotropinomas Are Associated With Greater Aggressiveness. J Clin Endocrinol Metab 2019, 104(5):1792-1801.
30. Corsello A, Ramunno V, Locantore P, Pacini G, Rossi ED, Torino F, Pontecorvi A, De Crea C, Paragliola RM, Raffaelli M, Corsello SM. Medullary Thyroid Cancer with Ectopic Cushing's Syndrome: A Case Report and Systematic Review of Detailed Cases from the Literature. Thyroid 2022, 32(11):1281-1298.
31. Agaimy A, Kasajima A, Stoehr R, Haller F, Schubart C, Togel L, Pfarr N, von Werder A, Pavel ME, Sessa F, Uccella S, La Rosa S, Kloppel G. Gene fusions are frequent in ACTH-secreting neuroendocrine neoplasms of the pancreas, but not in their non-pancreatic counterparts. Virchows Arch 2023, 482(3):507-516.
32. Wagner J, Portwine C, Rabin K, Leclerc JM, Narod SA, Malkin D. High frequency of germline p53 mutations in childhood adrenocortical cancer. J Natl Cancer Inst 1994, 86(22):1707-1710.
33. Latronico AC, Pinto EM, Domenice S, Fragoso MC, Martin RM, Zerbini MC, Lucon AM, Mendonca BB. An inherited mutation outside the highly conserved DNA-binding domain of the p53 tumor suppressor protein in children and adults with sporadic adrenocortical tumors. J Clin Endocrinol Metab 2001, 86(10):4970-4973.
34. Pinto EM, Billerbeck AE, Villares MC, Domenice S, Mendonca BB, Latronico AC. Founder effect for the highly prevalent R337H mutation of tumor suppressor p53 in Brazilian patients with adrenocortical tumors. Arq Bras Endocrinol Metabol 2004, 48(5):647-650.
35. Schneider K, Zelley K, Nichols KE, Garber J: Li-Fraumeni Syndrome. In: GeneReviews((R)). edn. Edited by Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A. Seattle (WA); 1993.
36. Goh G, Scholl UI, Healy JM, Choi M, Prasad ML, Nelson-Williams C, Kunstman JW, Korah R, Suttorp AC, Dietrich D, Haase M, Willenberg HS, Stalberg P, Hellman P, Akerstrom G, Bjorklund P, Carling T, Lifton RP. Recurrent activating mutation in PRKACA in cortisol-producing adrenal tumors. Nat Genet 2014, 46(6):613-617.
37. Drougat L, Settas N, Ronchi CL, Bathon K, Calebiro D, Maria AG, Haydar S, Voutetakis A, London E, Faucz FR, Stratakis CA. Genomic and sequence variants of protein kinase A regulatory subunit type 1beta (PRKAR1B) in patients with adrenocortical disease and Cushing syndrome. Genet Med 2021, 23(1):174-182.
38. Bonnet S, Gaujoux S, Launay P, Baudry C, Chokri I, Ragazzon B, Libe R, Rene-Corail F, Audebourg A, Vacher-Lavenu MC, Groussin L, Bertagna X, Dousset B, Bertherat J, Tissier F. Wnt/beta-catenin pathway activation in adrenocortical adenomas is frequently due to somatic CTNNB1-activating mutations, which are associated with larger and nonsecreting tumors: a study in cortisol-secreting and -nonsecreting tumors. J Clin Endocrinol Metab 2011, 96(2):E419-426.
39. Stratakis CA, Carney JA, Lin JP, Papanicolaou DA, Karl M, Kastner DL, Pras E, Chrousos GP. Carney complex, a

familial multiple neoplasia and lentiginosis syndrome. Analysis of 11 kindreds and linkage to the short arm of chromosome 2. J Clin Invest 1996, 97(3):699-705.
40. Kaltsas G, Kanakis G, Chrousos G: Carney Complex. In: Endotext. edn. Edited by Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J et al. South Dartmouth (MA); 2000.
41. Kirschner LS, Carney JA, Pack SD, Taymans SE, Giatzakis C, Cho YS, Cho-Chung YS, Stratakis CA. Mutations of the gene encoding the protein kinase A type I-alpha regulatory subunit in patients with the Carney complex. Nat Genet 2000, 26(1):89-92.
42. Stratakis CA, Jenkins RB, Pras E, Mitsiadis CS, Raff SB, Stalboerger PG, Tsigos C, Carney JA, Chrousos GP. Cytogenetic and microsatellite alterations in tumors from patients with the syndrome of myxomas, spotty skin pigmentation, and endocrine overactivity (Carney complex). J Clin Endocrinol Metab 1996, 81(10):3607-3614.
43. Espiard S, Vantyghem MC, Assie G, Cardot-Bauters C, Raverot G, Brucker-Davis F, Archambeaud-Mouveroux F, Lefebvre H, Nunes ML, Tabarin A, Lienhardt A, Chabre O, Houang M, Bottineau M, Stroer S, Groussin L, Guignat L, Cabanes L, Feydy A, Bonnet F, North MO, Dupin N, Grabar S, Duboc D, Bertherat J. Frequency and Incidence of Carney Complex Manifestations: A Prospective Multicenter Study With a Three-Year Follow-Up. J Clin Endocrinol Metab 2020, 105(3).
44. Horvath A, Mericq V, Stratakis CA. Mutation in PDE8B, a cyclic AMP-specific phosphodiesterase in adrenal hyperplasia. N Engl J Med 2008, 358(7):750-752.
45. Libe R, Fratticci A, Coste J, Tissier F, Horvath A, Ragazzon B, Rene-Corail F, Groussin L, Bertagna X, Raffin-Sanson ML, Stratakis CA, Bertherat J. Phosphodiesterase 11A (PDE11A) and genetic predisposition to adrenocortical tumors. Clin Cancer Res 2008, 14(12):4016-4024.
46. Lodish MB, Yuan B, Levy I, Braunstein GD, Lyssikatos C, Salpea P, Szarek E, Karageorgiadis AS, Belyavskaya E, Raygada M, Faucz FR, Izzat L, Brain C, Gardner J, Quezado M, Carney JA, Lupski JR, Stratakis CA. Germline PRKACA amplification causes variable phenotypes that may depend on the extent of the genomic defect: molecular mechanisms and clinical presentations. Eur J Endocrinol 2015, 172(6):803-811.
47. Carney JA, Lyssikatos C, Lodish MB, Stratakis CA. Germline PRKACA amplification leads to Cushing syndrome caused by 3 adrenocortical pathologic phenotypes. Hum Pathol 2015, 46(1):40-49.
48. Horvath A, Boikos S, Giatzakis C, Robinson-White A, Groussin L, Griffin KJ, Stein E, Levine E, Delimpasi G, Hsiao HP, Keil M, Heyerdahl S, Matyakhina L, Libe R, Fratticci A, Kirschner LS, Cramer K, Gaillard RC, Bertagna X, Carney JA, Bertherat J, Bossis I, Stratakis CA. A genome-wide scan identifies mutations in the gene encoding phosphodiesterase 11A4 (PDE11A) in individuals with adrenocortical hyperplasia. Nat Genet 2006, 38(7):794-800.
49. Espiard S, Drougat L, Libe R, Assie G, Perlemoine K, Guignat L, Barrande G, Brucker-Davis F, Doullay F, Lopez S, Sonnet E, Torremocha F, Pinsard D, Chabbert-Buffet N, Raffin-Sanson ML, Groussin L, Borson-Chazot F, Coste J, Bertagna X, Stratakis CA, Beuschlein F, Ragazzon B, Bertherat J. ARMC5 Mutations in a Large Cohort of Primary Macronodular Adrenal Hyperplasia: Clinical and Functional Consequences. J Clin Endocrinol Metab 2015, 100(6):E926-935.
50. Brown RJ, Kelly MH, Collins MT. Cushing syndrome in the McCune-Albright syndrome. J Clin Endocrinol Metab 2010, 95(4):1508-1515.
51. Dumitrescu CE, Collins MT. McCune-Albright syndrome. Orphanet J Rare Dis 2008, 3:12.
52. Carney JA, Ho J, Kitsuda K, Young WF, Jr., Stratakis CA. Massive neonatal adrenal enlargement due to cytomegaly, persistence of the transient cortex, and hyperplasia of the permanent cortex: findings in Cushing syndrome associated with hemihypertrophy. Am J Surg Pathol 2012, 36(10):1452-1463.
53. Schweiger BM, Esakhan CL, Frishberg D, Grand K, Garg R, Sanchez-Lara PA. Pediatric Cushing syndrome: An early sign of an underling cancer predisposition syndrome. Am J Med Genet A 2021, 185(9):2824-2828.
54. Magiakou MA, Mastorakos G, Oldfield EH, Gomez MT, Doppman JL, Cutler GB, Jr., Nieman LK, Chrousos GP. Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. N Engl J Med 1994, 331(10):629-636.
55. Greening JE, Storr HL, McKenzie SA, Davies KM, Martin L, Grossman AB, Savage MO. Linear growth and body mass index in pediatric patients with Cushing's disease or simple obesity. J Endocrinol Invest 2006, 29(10):885-887.
56. Keil MF, Graf J, Gokarn N, Stratakis CA. Anthropometric measures and fasting insulin levels in children before and after cure of Cushing syndrome. Clin Nutr 2012, 31(3):359-363.
57. Gunther DF, Bourdeau I, Matyakhina L, Cassarino D, Kleiner DE, Griffin K, Courkoutsakis N, Abu-Asab M, Tsokos M, Keil M, Carney JA, Stratakis CA. Cyclical Cushing syndrome presenting in infancy: an early form of primary pigmented nodular adrenocortical disease, or a new entity? J Clin Endocrinol Metab 2004, 89(7):3173-3182.
58. Lodish MB, Gourgari E, Sinaii N, Hill S, Libuit L, Mastroyannis S, Keil M, Batista DL, Stratakis CA. Skeletal maturation in children with Cushing syndrome is not consistently delayed: the role of corticotropin, obesity, and steroid hormones, and the effect of surgical cure. J Pediatr 2014, 164(4):801-806.

59. Stratakis CA, Mastorakos G, Mitsiades NS, Mitsiades CS, Chrousos GP. Skin manifestations of Cushing disease in children and adolescents before and after the resolution of hypercortisolemia. Pediatr Dermatol 1998, 15(4):253-258.
60. Leong GM, Abad V, Charmandari E, Reynolds JC, Hill S, Chrousos GP, Nieman LK. Effects of child- and adolescent-onset endogenous Cushing syndrome on bone mass, body composition, and growth: a 7-year prospective study into young adulthood. J Bone Miner Res 2007, 22(1):110-118.
61. Lodish MB, Hsiao HP, Serbis A, Sinaii N, Rothenbuhler A, Keil MF, Boikos SA, Reynolds JC, Stratakis CA. Effects of Cushing disease on bone mineral density in a pediatric population. J Pediatr 2010, 156(6):1001-1005.
62. Ward LM. Glucocorticoid-Induced Osteoporosis: Why Kids Are Different. Front Endocrinol (Lausanne) 2020, 11:576.
63. Merke DP, Giedd JN, Keil MF, Mehlinger SL, Wiggs EA, Holzer S, Rawson E, Vaituzis AC, Stratakis CA, Chrousos GP. Children experience cognitive decline despite reversal of brain atrophy one year after resolution of Cushing syndrome. J Clin Endocrinol Metab 2005, 90(5):2531-2536.
64. Ferrau F, Korbonits M. Metabolic comorbidities in Cushing's syndrome. Eur J Endocrinol 2015, 173(4):M133-157.
65. Lodish M, Patronas NJ, Stratakis CA. Reversible posterior encephalopathy syndrome associated with micronodular adrenocortical disease and Cushing syndrome. Eur J Pediatr 2010, 169(1):125-126.
66. Birdwell L, Lodish M, Tirosh A, Chittiboina P, Keil M, Lyssikatos C, Belyavskaya E, Feelders RA, Stratakis CA. Coagulation Profile Dynamics in Pediatric Patients with Cushing Syndrome: A Prospective, Observational Comparative Study. J Pediatr 2016, 177:227-231.
67. Wagner J, Langlois F, Lim DST, McCartney S, Fleseriu M. Hypercoagulability and Risk of Venous Thromboembolic Events in Endogenous Cushing's Syndrome: A Systematic Meta-Analysis. Front Endocrinol (Lausanne) 2018, 9:805.
68. Wurth R, Rescigno M, Flippo C, Stratakis CA, Tatsi C. Inflammatory biomarkers in the evaluation of pediatric endogenous Cushing syndrome. Eur J Endocrinol 2022, 186(4):503-510.
69. Tatsi C, Boden R, Sinaii N, Keil M, Lyssikatos C, Belyavskaya E, Rosenzweig SD, Stratakis CA, Lodish MB. Decreased lymphocytes and increased risk for infection are common in endogenous pediatric Cushing syndrome. Pediatr Res 2018, 83(2):431-437.
70. Gkourogianni A, Lodish MB, Zilbermint M, Lyssikatos C, Belyavskaya E, Keil MF, Stratakis CA. Death in pediatric Cushing syndrome is uncommon but still occurs. Eur J Pediatr 2015, 174(4):501-507.
71. Rahman SH, Papadakis GZ, Keil MF, Faucz FR, Lodish MB, Stratakis CA. Kidney Stones as an Underrecognized Clinical Sign in Pediatric Cushing Disease. J Pediatr 2016, 170:273-277 e271.
72. Weinberg JR, Voudouri M, Keil M, Stratakis CA, Tatsi C. The utility of IGF1 in the evaluation of pediatric patients with endogenous hypercortisolemia. Pediatr Res 2023.
73. Stratakis CA, Mastorakos G, Magiakou MA, Papavasiliou E, Oldfield EH, Chrousos GP. Thyroid function in children with Cushing's disease before and after transsphenoidal surgery. J Pediatr 1997, 131(6):905-909.
74. Unuane D, Tournaye H, Velkeniers B, Poppe K. Endocrine disorders & female infertility. Best Pract Res Clin Endocrinol Metab 2011, 25(6):861-873.
75. Magiakou MA, Mastorakos G, Gomez MT, Rose SR, Chrousos GP. Suppressed spontaneous and stimulated growth hormone secretion in patients with Cushing's disease before and after surgical cure. J Clin Endocrinol Metab 1994, 78(1):131-137.
76. Fleseriu M, Auchus R, Bancos I, Ben-Shlomo A, Bertherat J, Biermasz NR, Boguszewski CL, Bronstein MD, Buchfelder M, Carmichael JD, Casanueva FF, Castinetti F, Chanson P, Findling J, Gadelha M, Geer EB, Giustina A, Grossman A, Gurnell M, Ho K, Ioachimescu AG, Kaiser UB, Karavitaki N, Katznelson L, Kelly DF, Lacroix A, McCormack A, Melmed S, Molitch M, Mortini P, Newell-Price J, Nieman L, Pereira AM, Petersenn S, Pivonello R, Raff H, Reincke M, Salvatori R, Scaroni C, Shimon I, Stratakis CA, Swearingen B, Tabarin A, Takahashi Y, Theodoropoulou M, Tsagarakis S, Valassi E, Varlamov EV, Vila G, Wass J, Webb SM, Zatelli MC, Biller BMK. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol 2021.
77. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2008, 93(5):1526-1540.
78. Babic N, Yeo KTJ, Hannoush ZC, Weiss RE: Endocrine Testing Protocols: Hypothalamic Pituitary Adrenal Axis. In: Endotext. edn. Edited by Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J et al. South Dartmouth (MA); 2000.
79. Newell-Price J, Trainer P, Perry L, Wass J, Grossman A, Besser M. A single sleeping midnight cortisol has 100% sensitivity for the diagnosis of Cushing's syndrome. Clin Endocrinol (Oxf) 1995, 43(5):545-550.
80. Tatsi C, Stratakis C: Cushing Disease: Diagnosis and Treatment. In: Pituitary Disorders of Childhood Diagnosis and Clinical Management. edn. Edited by Kohn B: Springer Nature Switzerland AG; 2019: 89-114.
81. Carroll T, Raff H, Findling JW. Late-night salivary cortisol for the diagnosis of Cushing syndrome: a meta-analysis. Endocr Pract 2009, 15(4):335-342.
82. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome

and pseudo-Cushing's states. Endocr Rev 1998, 19(5):647-672.
83. Stratakis CA. An update on Cushing syndrome in pediatrics. Ann Endocrinol (Paris) 2018, 79(3):125-131.
84. Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M, Sen K, Salgado LR, Colao A, Biller BM, Pasireotide BSG. High variability in baseline urinary free cortisol values in patients with Cushing's disease. Clin Endocrinol (Oxf) 2014, 80(2):261-269.
85. Luger A, Deuster PA, Kyle SB, Gallucci WT, Montgomery LC, Gold PW, Loriaux DL, Chrousos GP. Acute hypothalamic-pituitary-adrenal responses to the stress of treadmill exercise. Physiologic adaptations to physical training. N Engl J Med 1987, 316(21):1309-1315.
86. Mericq MV, Cutler GB, Jr. High fluid intake increases urine free cortisol excretion in normal subjects. J Clin Endocrinol Metab 1998, 83(2):682-684.
87. Bertrand PV, Rudd BT, Weller PH, Day AJ. Free cortisol and creatinine in urine of healthy children. Clin Chem 1987, 33(11):2047-2051.
88. Hindmarsh PC, Brook CG. Single dose dexamethasone suppression test in children: dose relationship to body size. Clin Endocrinol (Oxf) 1985, 23(1):67-70.
89. Ferrigno R, Hasenmajer V, Caiulo S, Minnetti M, Mazzotta P, Storr HL, Isidori AM, Grossman AB, De Martino MC, Savage MO. Paediatric Cushing's disease: Epidemiology, pathogenesis, clinical management and outcome. Rev Endocr Metab Disord 2021, 22(4):817-835.
90. Findling JW, Raff H. DIAGNOSIS OF ENDOCRINE DISEASE: Differentiation of pathologic/neoplastic hypercortisolism (Cushing's syndrome) from physiologic/non-neoplastic hypercortisolism (formerly known as pseudo-Cushing's syndrome). Eur J Endocrinol 2017, 176(5):R205-R216.
91. Tatsi C, Bompou ME, Flippo C, Keil M, Chittiboina P, Stratakis CA. Paediatric patients with Cushing disease and negative pituitary MRI have a higher risk of nonremission after transsphenoidal surgery. Clin Endocrinol (Oxf) 2021, 95(6):856-862.
92. Frete C, Corcuff JB, Kuhn E, Salenave S, Gaye D, Young J, Chanson P, Tabarin A. Non-invasive Diagnostic Strategy in ACTH-dependent Cushing's Syndrome. J Clin Endocrinol Metab 2020, 105(10).
93. Varlamov E, Hinojosa-Amaya JM, Stack M, Fleseriu M. Diagnostic utility of Gallium-68-somatostatin receptor PET/CT in ectopic ACTH-secreting tumors: a systematic literature review and single-center clinical experience. Pituitary 2019, 22(5):445-455.
94. Courcoutsakis NA, Tatsi C, Patronas NJ, Lee CC, Prassopoulos PK, Stratakis CA. The complex of myxomas, spotty skin pigmentation and endocrine overactivity (Carney complex): imaging findings with clinical and pathological correlation. Insights Imaging 2013, 4(1):119-133.
95. Stratakis CA, Sarlis N, Kirschner LS, Carney JA, Doppman JL, Nieman LK, Chrousos GP, Papanicolaou DA. Paradoxical response to dexamethasone in the diagnosis of primary pigmented nodular adrenocortical disease. Ann Intern Med 1999, 131(8):585-591.
96. Chen J, Liu H, Man S, Liu G, Li Q, Zuo Q, Huo L, Li W, Deng W. Endoscopic vs. Microscopic Transsphenoidal Surgery for the Treatment of Pituitary Adenoma: A Meta-Analysis. Front Surg 2021, 8:806855.
97. Broersen LHA, Biermasz NR, van Furth WR, de Vries F, Verstegen MJT, Dekkers OM, Pereira AM. Endoscopic vs. microscopic transsphenoidal surgery for Cushing's disease: a systematic review and meta-analysis. Pituitary 2018, 21(5):524-534.
98. Marino AC, Taylor DG, Desai B, Jane JA, Jr. Surgery for Pediatric Pituitary Adenomas. Neurosurg Clin N Am 2019, 30(4):465-471.
99. Luzzi S, Giotta Lucifero A, Rabski J, Kadri PAS, Al-Mefty O. The Party Wall: Redefining the Indications of Transcranial Approaches for Giant Pituitary Adenomas in Endoscopic Era. Cancers (Basel) 2023, 15(8).
100. Ironside N, Chatain G, Asuzu D, Benzo S, Lodish M, Sharma S, Nieman L, Stratakis CA, Lonser RR, Chittiboina P. Earlier post-operative hypocortisolemia may predict durable remission from Cushing's disease. Eur J Endocrinol 2018, 178(3):255-263.
101. Ram Z, Nieman LK, Cutler GB, Jr., Chrousos GP, Doppman JL, Oldfield EH. Early repeat surgery for persistent Cushing's disease. J Neurosurg 1994, 80(1):37-45.
102. Yordanova G, Martin L, Afshar F, Sabin I, Alusi G, Plowman NP, Riddoch F, Evanson J, Matson M, Grossman AB, Akker SA, Monson JP, Drake WM, Savage MO, Storr HL. Long-term outcomes of children treated for Cushing's disease: a single center experience. Pituitary 2016, 19(6):612-624.
103. Batista DL, Oldfield EH, Keil MF, Stratakis CA. Postoperative testing to predict recurrent Cushing disease in children. J Clin Endocrinol Metab 2009, 94(8):2757-2765.
104. Savage MO, Chan LF, Grossman AB, Storr HL. Work-up and management of paediatric Cushing's syndrome. Curr Opin Endocrinol Diabetes Obes 2008, 15(4):346-351.
105. Meloche-Dumas L, Mercier F, Lacroix A. Role of unilateral adrenalectomy in bilateral adrenal hyperplasias with Cushing's syndrome. Best Pract Res Clin Endocrinol Metab 2021, 35(2):101486.
106. Castinetti F. Cushing's disease: role of preoperative and primary medical therapy. Pituitary 2022, 25(5):737-739.
107. Castinetti F, Brue T, Ragnarsson O. Radiotherapy as a tool for the treatment of Cushing's disease. Eur J Endocrinol 2019, 180(5):D9-D18.
108. Geer EB, Ayala A, Bonert V, Carmichael JD, Gordon MB, Katznelson L, Manuylova E, Shafiq I, Surampudi V,

Swerdloff RS, Broder MS, Cherepanov D, Eagan M, Lee J, Said Q, Neary MP, Biller BMK. Follow-up intervals in patients with Cushing's disease: recommendations from a panel of experienced pituitary clinicians. Pituitary 2017, 20(4):422-429.

109. Reincke M, Fleseriu M. Cushing Syndrome: A Review. JAMA 2023, 330(2):170-181.

110. Tatsi C, Neely M, Flippo C, Bompou ME, Keil M, Stratakis CA. Recovery of hypothalamic-pituitary-adrenal axis in paediatric Cushing disease. Clin Endocrinol (Oxf) 2021, 94(1):40-47.

111. Zhang CD, Li D, Singh S, Suresh M, Thangamuthu K, Nathani R, Achenbach SJ, Atkinson EJ, Van Gompel JJ, Young WF, Bancos I. Glucocorticoid withdrawal syndrome following surgical remission of endogenous hypercortisolism: a longitudinal observational study. Eur J Endocrinol 2023, 188(7):592-602.