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CUSHING SYNDROME IN PEDIATRICS

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Abstract

Cushing syndrome (CS) is a multisystem disorder that results from the prolonged exposure to excess glucocorticoids. It is characterized by growth deceleration, weight gain, truncal obesity, facial plethora, and hypertension. In children, CS most commonly results from the exogenous administration of steroids. Endogenous causes of CS are rare, and include ACTH overproduction from a pituitary adenoma, or adrenal hypersecretion of cortisol secondary to an adenoma, carcinoma, or hyperplasia; ectopic causes are rare. Clinical practice guidelines, including diagnostic algorithms are available to assist clinicians; patients should be referred to multidisciplinary centers of excellence with experience in endocrinology and surgery. CS in children may be associated with distinct germline and somatic mutations. Early detection and treatment is essential to reduce associated acute and long-term morbidity and potential death.

Keywords

Cushing syndrome; Pituitary tumors; Adrenal cortex; Carney complex; Adrenocortical hyperplasia; Adrenal cancer

EPIDEMIOLOGY AND ETIOLOGY

Endogenous Cushing syndrome (CS) is a rare multisystem disorder that results from overproduction of the glucocorticoid hormone cortisol whether due to ACTH-dependent of ACTH-independent cause. In contrast, “exogenous” or “iatrogenic” Cushing syndrome occurs when glucocorticoids in the form of medications such as prednisone, which are commonly used for inflammatory disorders, are given in high enough doses for prolonged periods of time. The overall incidence of endogenous CS is 0.7–2.4 per million people per year.[1] Only approximately 10% of the new cases each year occur in children. In both adults and children, CS is most commonly caused by an ACTH-secreting pituitary tumor.

Under normal conditions cortisol is secreted from the cortical cells of the adrenal glands under the control of the pituitary hormone ACTH (adrenocorticotropic hormone). Corticotropin (ACTH)-releasing hormone (CRH) is synthesized in the hypothalamus and

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carried to the anterior pituitary in the portal system. CRH stimulates Adrenocorticotropic hormone (ACTH) release from the anterior pituitary, which in turn stimulates the adrenal cortex to secrete cortisol (hypothalamic-pituitary-adrenal or HPA axis)[2,3] Cortisol inhibits the secretion of primarily CRH and secondarily ACTH in a negative feedback regulation system. In CS, the HPA axis has lost its ability for self-regulation, due to excessive secretion of either ACTH or cortisol and the loss of the negative feedback function. Diagnostic tests, on the other hand, take advantage of the tight regulation of the HPA axis in the normal state and its disturbance in CS to guide therapy toward the primary cause of this disorder[4,5].

Cushing disease (CD) results from overproduction of ACTH by a pituitary adenoma which in turn results in overproduction of cortisol from the adrenal cortex and a state of hypercortisolism. Other forms of CS are due to autonomous production of cortisol from adrenal cortical tumors, or ectopic ACTH syndrome (overproduction of ACTH from a non-pituitary tumor). CD and the ectopic ACTH syndrome are often referred to as ACTH-dependent CS, whereas adrenal cortical tumors cause ACTH-independent CS. Approximately 75-90% of CS cases in children are due to CD. CD is uncommon in children under 6 years of age; adrenal causes of CS (adenoma, carcinoma, or bilateral hyperplasia) are the typical etiologies in younger children.

Autonomous secretion of cortisol from the adrenal glands, or ACTH-independent CS, accounts for approximately 15% of all the cases of CS in childhood. CS is a manifestation of approximately one-third of all adrenal tumors. In adrenal cancer, adrenal adenomas, bilateral micronodular adrenal hyperplasia, and primary bilateral macronodular adrenocortical hyperplasia, a spectrum of tumor growth exists as a result of a variety of genetic defects that have been recently identified. Details surrounding the genetics of pituitary and adrenal tumors associated with Cushing syndrome are discussed in a separate chapter.

The annual incidence of pediatric adrenocortical carcinoma according to the SEER database from 1973 through 2008 was 0.21 per million.[6] Adrenocortical carcinoma has a bimodal age distribution, with a peak in early childhood at 3 years[7], and a peak in adulthood in the 40s and 50s[8]. These tumors are characterized by poor survival, especially in the context of distant metastases, large tumor volume, and older age.[9] Adrenocortical cancers in childhood may be associated with the Li–Fraumeni or Beckwith–Wiedemann syndromes, and rarely with adenomatous polyposis coli and other rare genetic conditions.

Defects in cAMP signaling underlie the majority of cortisol-producing adrenal hyperplasia and tumors.[10] McCune Albright Syndrome, in which a somatic mutation of the *GNAS1* gene leads to constitutive activation of the Gsa Protein, may be associated with infantile Cushing syndrome[11]. Primary pigmented adrenocortical nodular disease (PPNAD) is a genetic disorder usually associated with Carney complex, a syndrome of multiple endocrine gland abnormalities in addition to myxomas and lentigines[12]. The adrenal glands in PPNAD are characterized by multiple pigmented nodules that autonomously secrete cortisol, and are surrounded by an atrophic cortex. Children and adolescents with PPNAD frequently have periodic or cyclical CS. The underlying genetic defect in most forms of PPNAD is mutations of the *PRKAR1A* gene coding for the regulatory type I-alpha subunit of protein kinase A (PKA).[13]

Ectopic ACTH production occurs rarely in young children, accounting for less than 1% of the cases of CS in adolescents[14]. Sources of ectopic ACTH include, carcinoid tumors in the bronchus, pancreas, or thymus; medullary carcinomas of the thyroid, small cell carcinoma of the lung, pheochromocytomas; and other pancreatic and gastrointestinal neuroendocrine tumors. Ectopic ACTH/CRH co-secreting tumors are also extremely rare in children and adolescents. The diagnosis of this condition is frequently missed and is sometimes confused with CD due to the effect of CRH on the pituitary[15].

CLINICAL PRESENTATION

In most children, the onset of CS is insidious.[2–4] The most common presenting symptom is weight gain; in childhood, lack of height gain concomitant with weight gain is the most common presentation of CS. A growth chart typical for a child with CS is shown in Fig. 1. Other common presenting signs and symptoms of CS in children are listed in Table 1 [2,16–19].

DIAGNOSTIC GUIDELINES

Accurate diagnosis and classification of CS is crucial for determining the appropriate therapeutic intervention. The clinical evaluation and medical history, especially review of growth data, are important to make the initial diagnosis. Upon suspicion of CS, laboratory and imaging confirmations are necessary. An algorithm of the diagnostic process is presented in Fig. 2. The Endocrine Society published guidelines on the diagnostic workup of CS in 2008[5].

The first step in the diagnosis of CS is documentation of hypercortisolism, typically with 24-hour urinary free cortisol (UFC) with at least 2, preferably 3 consecutive collections (correct for body surface area); late-night salivary cortisol; and/or a low-dose dexamethasone-suppression test (DST) (1 mg overnight or 2 mg/day over 48 hours). None of these tests has 100% diagnostic accuracy; each test has its own limitations, and multiple tests are usually needed to establish the diagnosis. In some studies, late-night salivary cortisol has been shown to have superior diagnostic performance to UFC, and it has been shown to be a simple, accurate way to screen for hypercortisolism in children[20–22], however there is much variation in laboratory performance of this test. Recently, hair cortisol has been used as an additional measure of evaluating patients with suspected CS[23]. 24- hour UFC measurement can be challenging and false positive elevations can be caused due to pseudo-cushing states including physical and emotional stress, chronic and severe obesity, pregnancy, chronic exercise, depression, poor diabetes control, alcoholism, anorexia, narcotic withdrawal, anxiety, malnutrition, and high water intake. Conversely, inadequate collection of urine may lead to falsely low UFC levels. Measuring cortisol at midnight with an indwelling IV is the gold standard for documenting hypercortisolemia, a midnight cortisol value of greater than 4.4 mg/dL has a high sensitivity and specificity for CS[4]. However, diurnal testing requires an inpatient stay and its use as a routine screening test is limited.

Once the diagnosis of CS is confirmed, there are several tests to distinguish ACTH-dependent from the ACTH-independent disease. A spot morning plasma ACTH of greater than or equal to 29 pg/mL in children with confirmed CS has a sensitivity of 70% in

identifying children with an ACTH-dependent form of the syndrome[4]. The standard high-dose dexamethasone suppression test (HDDST or Liddle test) is used to differentiate CD from ectopic ACTH secretion and adrenal causes of CS. In this test, 120 mg/kg (maximum dose 8 mg) of dexamethasone is administered at 11 PM and plasma cortisol is measured at 9 AM the morning before and the morning following the dexamethasone. In children, a 20% cortisol suppression from baseline had sensitivity and specificity of 97.5% and 100%, respectively, with the HDDST for differentiating patients with CD from those with adrenal tumors[4]. An oCRH stimulation test may also be obtained for the differentiation of CD from ectopic ACTH secretion and/or adrenal lesions. The criterion for diagnosis of CD is a mean increase of 20% above baseline for cortisol values at 30 and 45 minutes and an increase in the mean corticotropin concentrations of at least 35% over basal value at 15 and 30 minutes after CRH administration[24]. If bilateral adrenocortical hyperplasia is suspected, the classic Liddle's test (low- dose dexamethasone of 30 ug/kg/dose; maximum 0.5 mg/dose) every 6 hours for 8 doses for 8 doses; followed by the high dose dexamethasone (120 ug/kg/dose, maximum 2 mg/dose) every 6 hours for 8 doses) may be used. This test shows a paradoxical stimulation of cortisol secretion in PPNAD[25].

Diagnostic imaging is another important tool in the localization and characterization of CS.

- Pituitary magnetic resonance imaging (MRI) in thin sections (1-2mm) with high resolution and with contrast (gadolinium).
- High-resolution[18] FDG PET for detection of small functioning corticotrophs adenomas[26].
- Adrenal CT scan is useful in the distinction between Cushing disease and adrenal causes of Cushing syndrome.
- CT or MRI scan of the neck, chest, abdomen, and pelvis may be used for the detection of an ectopic source of ACTH production.
- Labeled octreotide scanning, positron-emission tomography (PET), and/or 68Ga-DOTATATE PET/CT may help in the localization of an ectopic ACTH source.
- If the biochemical workup is not definitive for a pituitary source, and/or if a lesion is not visible on pituitary MRI, bilateral inferior petrosal sinus sampling (IPSS) has been used for the localization of a pituitary microadenoma[27].

TREATMENT

In 2015, the Endocrine Society published clinical practice guidelines for treating Cushing syndrome, however they are not specific for children[24]. Transsphenoidal surgical (TSS) resection of the ACTH secreting pituitary tumor remains the first line therapeutic intervention in CD. In specialized centers with experienced neurosurgeons, the success rate of the first TSS is close to or even higher than 90%[28,29]. Pituitary surgery may not be successful, and disease may recur years after initial surgery. The success rate of repeat TSS is lower than the initial surgery, closer to 60%. Postoperative complications include diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion, central hypothyroidism, hypogonadism, growth hormone deficiency, bleeding, infection, and

pituitary apoplexy. The mortality rate is extremely low, at less than 1%. For those patients not achieving an initial remission or developing recurrence after an initial remission, therapeutic options are limited.

Pituitary radiotherapy often used in adults is generally avoided in children, especially those who are prepubertal, due to complications of radiation (cerebral cortex toxicity, hypopituitarism). However, in children, conventional RT without adjunctive medical treatment should take effect more rapidly than in adults[30]. Unfortunately, hypopituitarism is a common complication of RT and pituitary function requires frequent assessment[31]. The traditional dose of RT is 4500–5000 cGy given over a 6-week period. However, innovative types of stereotactic radiotherapy are now available for the treatment of CD, including linear particle accelerator (LINAC), Gamma Knife stereotactic radiosurgery (SRS), and proton beam therapy. While large pediatric studies are not available, literature from adults shows that SRS provides an effective and tolerated treatment option for patients with pituitary adenomas. SRS offers the benefit of more rapid treatment and the potential for reduced side-effects. In a recent retrospective review of 262 patients treated with SRS, tumor control rate was 89%; higher margin radiation dose to the adenoma and suprasellar extension were two independent predictors of SRS-induced hypopituitarism[32]. In a long-term study of radiation therapy in pituitary adenomas, including individuals as young as age 10, radiation therapy was seen to increase the quality of life in 95% of patients, and local progression-free survival following radiation therapy was 90% at 2 years[33]. It is important to realize that SRS may lead to radiation- induced optic neuropathy and associated blindness when the dose to the anterior visual pathway is greater than 8Gy[34].

Currently, medical therapy for CD serves primarily in an adjunctive role after unsuccessful pituitary surgery. There are three mechanisms of action for drugs used in medical therapy: modulation of ACTH release, inhibition of adrenal steroidogenesis and glucocorticoid receptor (GR) blockade. Until recently there had been no medications approved by the U.S. Food and Drug administration (FDA) for use in CD, which led to off label use of some drugs, most commonly ketoconazole. Table 2 lists current options for medical therapy[24,35]. There is very limited experience using ketoconazole or other therapeutics in the medical treatment of pediatric patients with CS.

Benign adrenal tumors are best treated with surgical resection; in the case of bilateral micronodular or macronodular adrenal disease, bilateral total adrenalectomy is the preferred treatment. Treatment guidelines for children with adrenal cancer are lacking because of the rarity of this disease, a recent Children’s Oncology Group trial evaluating cisplatin, etoposide, and doxorubicin combined with surgery showed an excellent outcome for stage III ACC, but poor outcome with stage IV ACC[36].

Adrenalectomy is an option for refractory CD or ACTH-dependent CS. Early bilateral adrenalectomy in patients with uncontrolled CS may improve adverse events[37]. However, a potential complication after bilateral adrenalectomy in patients with CD is growth of the corticotropinoma, elevated ACTH levels, and hyperpigmentation (Nelson’s syndrome). Recent approximations from two systematic reviews in adults found that Nelson’s syndrome

occurred in 21–24% of the patients[38]. Adrenal crisis is another lifelong risk in these individuals.

GLUCOCORTICOID REPLACEMENT

After the completion of successful TSS in CD or excision of an autonomously functioning adrenal adenoma, there will be a period of adrenal insufficiency while the hypothalamic pituitary adrenal axis is recovering. During this period, glucocorticoid should be replaced at the suggested physiologic replacement dose (12–15 mg/m2/day 2 or 3 times daily), as we have recently published[39]. In the immediate postoperative period, stress doses of cortisol should be initiated. This should be weaned relatively rapidly to a physiologic replacement dose, and followed every few months; the adrenocortical function should be periodically assessed with a 1-hour ACTH test (normal response is a cortisol level over 18 ug/dL at 30 or 60 minutes after ACTH stimulation)[39] and the glucocorticoid dose tapered. Average time to recovery of the HPA axis post-TSS in children is 12.6±3 months; early recovery of HPA axis (<6 months) is associated with recurrence.[39]

After bilateral adrenalectomy, patients require lifetime replacement with both glucocorticoids (as described previously) and mineralocorticoids (fludrocortisone 0.1–0.3 mg daily). These patients also need stress doses of glucocorticoids in the immediate postoperative period; and should be weaned to physiologic replacement relatively quickly.

In addition, stress dosing for acute illness, trauma, or surgical p r o c ed u r es is required for both temporary and permanent adrenal insufficiency[24]. Adrenal crisis, which is associated with increased morbidity and mortality[40,41] highlights the importance of ongoing patient and caregiver education[41,42].

MEDICAL, PSYCHOSOCIAL, AND COGNITIVE OUTCOMES

CS in childhood has the potential for long-term adverse medical outcomes due to prolonged exposure of the body to high levels of glucocorticoids as well as morbidity associated with surgical or radiation treatment[7,9,17,31,43]. Table 2 lists treatment and long-term clinical effects of CS in childhood[2,9,17,31,44–46]. We recently reported disparities related to delayed diagnosis and treatment in non-white populations that was associated with higher risk for persistent CD or recurrent CD after surgery[47]. Post-treatment challenges for the child or adolescent treated for CS include optimize growth and pubertal development, normalize body composition, and promote psychological health and cognitive development[48]. We recently reported that systolic hypertension persisted in 16% of CD and 21% of ACTH-independent CS, and diastolic hypertension was noted in approximately 4% of all pediatric patients 1-year after cure[49]. Adverse effects of abdominal adiposity, insulin resistance, hypertension, and cardiovascular dysfunction may persist after cure of CS[18]. Studies of final height and catch-up growth after treatment of CS have shown conflicting results; children with poorer than expected catch up growth should be tested to confirm ongoing remission of hypercortisolemia and evaluation of GH axis recovery[45,50,51].

CS has been associated with multiple psychiatric and psychological disturbances, most co mmon l y emotional lability, depression, and/or anxiety[2,51–53] (Table 3). Significant

psychopathology may remain after remission of hypercortisolism and even after recovery of the HPA axis[52,54]. The author and colleagues recently reported that children with CS may experience a decline i n cognitive a n d school performance 1- year after surgical cure, without any associated psychopathology, with younger age at first evaluation associated with greater deterioration in IQ scores[53,55]. Also, we recently reported that active CS, particularly in younger children, was associated with impaired quality of life scores and that despite improvement from before to 1 year after cure, residual impairment remained[55]. Although most self-reported CS symptoms showed improvement, forgetfulness, unclear thinking, and decreased attention span did not improve after cure[55].

Suicidal ideation has been reported in adults (~17%) with active CS and we recently reported suicidal ideation in approximately 6% of children after surgical cure of CS[52,56]. Normalization of the HPA axis may unveil or trigger psychopathological manifestations not precipitated by hypercortisolemia or vice versa. This highlights the importance of screening for risk factors for suicide and suicide ideation in children before and after treatment of CS. Patients and their caregivers should be advised that they may experience changes in mood, behavior, cognitive function, and quality of life for months or years after surgical cure of CS. Early recognition of Cushing syndrome in children is imperative; late diagnosis is associated with significant morbidity and mortality[43,47,48].

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Key Points

- Cushing syndrome in childhood results mostly from the exogenous administration of glucocorticoids; endogenous Cushing syndrome is a rare disease.
- In childhood, lack of height gain concomitant with weight gain is the most common presentation of Cushing syndrome.
- The first step in the diagnosis of Cushing syndrome is documentation of hypercortisolism with the 24- hour urinary free cortisol, late-night salivary cortisol, or a low-dose dexamethasone-suppression test.
- In children over the age of six years, Cushing syndrome is most commonly caused by an ACTH-secreting pituitary tumor, in children less than 6years old, adrenal causes are more common etiology of Cushing syndrome.
- Once the diagnosis of Cushing syndrome is confirmed, algorithms for testing to distinguish ACTH-dependent disease from the ACTH-independent syndrome are available. Surgery is the first line treatment intervention.

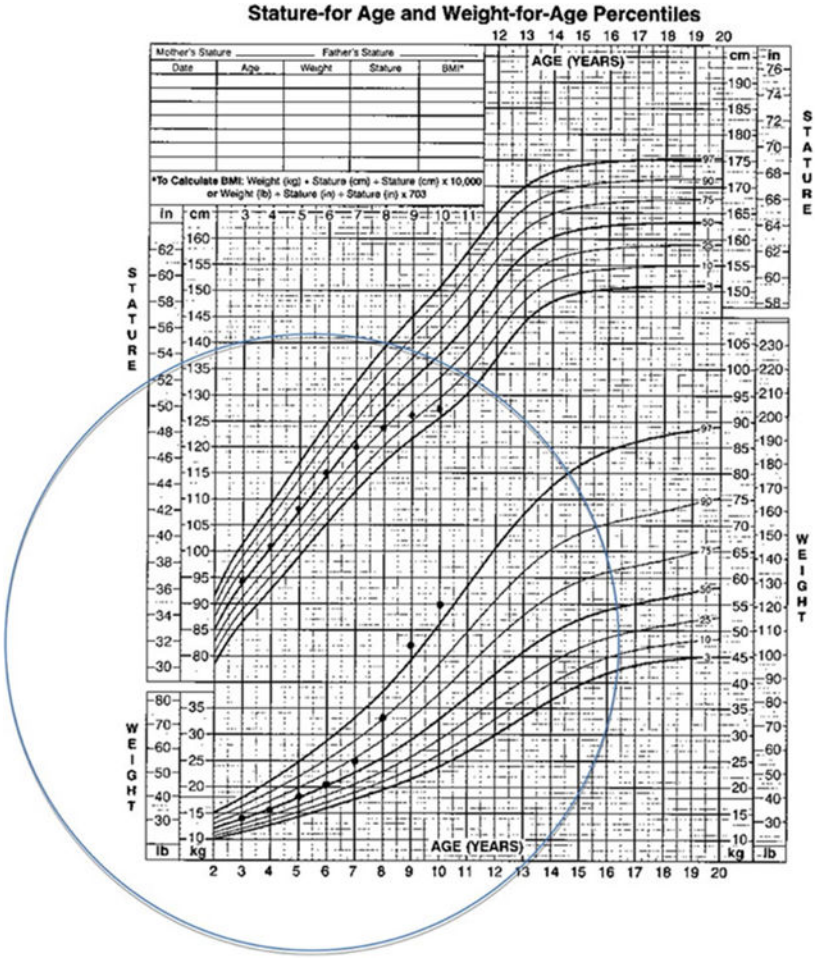

Fig 1.

Typical growth chart for a child with Cushing syndrome Linear height deceleration with concomitant weight gain starting at age 8years. From Constantine A. Stratakis. Cushing Syndrome in Pediatrics. Endocrinology and Metabolism Clinics of North America. Volume 41, Issue 4, December 2012, Pages 793-803, with permission.

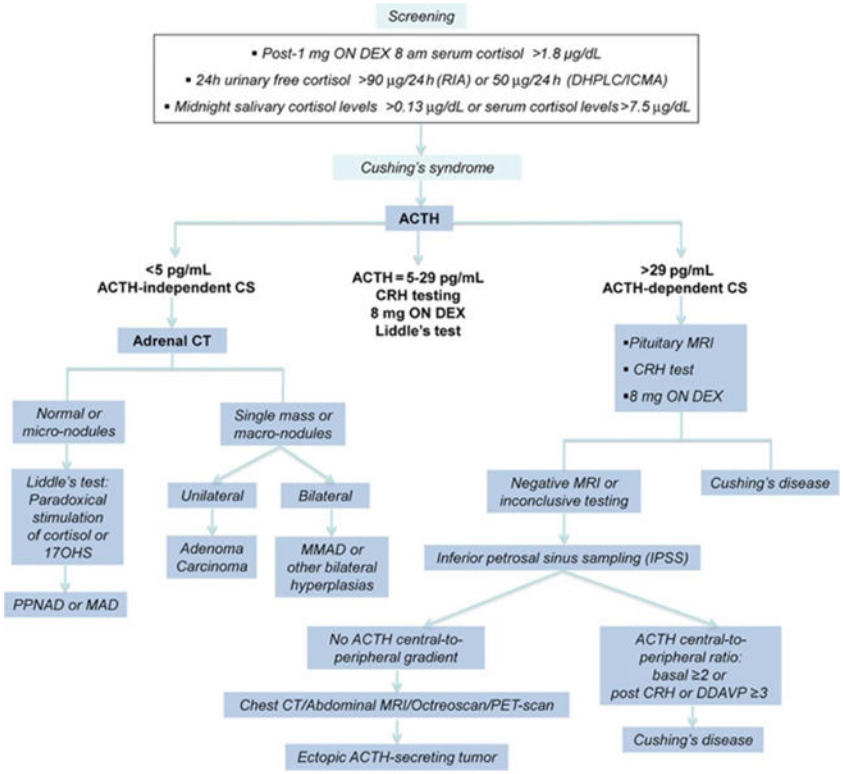

Fig 2.

Diagnostic algorithm in Cushing syndrome Screening for hypercortsolemia includes 1mg overnight (ON) dexamethasone (DEX), 24hr urine free cortisol, or midnight salivary cortisol. ACTH level is used to differentiate ACTH-independent vs. ACTH-independent CS and appropriate testing to confirm etiology of CS. From Constantine A. Stratakis. Cushing Syndrome in Pediatrics. Endocrinology and Metabolism Clinics of North America. Volume 41, Issue 4, December 2012, Pages 793-803, with permission.

Table 1

Presenting signs and symptoms of Cushing Syndrome in children

Dermatologic	Facial plethora, acne, acanthosis nigricans, easy bruising, supra-termoral and supra-clavicular fat pads, moon facies, fungal infection, hirsutism, fine downy hair, violaceous striae (unusual in children <7yrs age)
Neurological	headaches
Cardiovascular	Hypertension, coagulopathy
Growth	Growth deceleration with concomitant weight gain, central obesity,
Gonadal	Amenorrhea, virilization, gynecomastia
Other	Nephrolithiasis, bone fractures, impaired glucose tolerance, type two diabetes
Psychological	Depression, anxiety, mood swings, irritability, fatigue

Table 2

Medical treatment of Cushing syndrome

	Mechanism of action	Side effects	FDA/EMA approval
Ketoconazole	Antifungal azole inhibits steroidogenesis	Gastrointestinal side effects, hepatotoxicity, breakthrough requiring dose escalation, adrenal insufficiency	European Medicines Agency for adults
Mitotane	Adrenolytic	Gastrointestinal side effects, fatigue, dermatologic changes	FDA approval for treatment of adrenal cancer
Pasireotide	Somatostatin analog	Adrenal insufficiency, hyperglycemia, bradycardia, gastrointestinal side effects, hepatotoxicity, fatigue, headache	FDA approval for adults with CS who are not surgical candidates
Mifepristone	Glucocorticoid receptor blocker	Hypokalemia, adrenal insufficiency, endometrial thickening	FDA approval for adults with CS with diabetes or glucose intolerance who are not surgical candidates

Table 3

Long-term effects of Cushing syndrome in childhood

Treatment related	**Comorbidity**
Transsphenoidal surgery	Panhypopituitarism (partial or complete), pseudotumor cerebri, recurrence of CS
Pituitary irradiation	Panhypopituitarism (partial or complete), cranial neuropathies, radiation-induced tumors, cognitive decrement
Adrenalectomy	Adrenal insufficiency, Nelson syndrome
Pharmacological therapy	Recurrence of CS, hepatotoxicity, hypertension, hypokalemia, endometrial hyperplasia
Long – term clinical effects	
Growth	Compromised final height
Metabolic	Increased BMI, visceral obesity, impaired glucose metabolism, hyperlipidemia
Cardiovascular	Hypertension, increased arterial rigidity
Neuropsychiatric	Cerebral atrophy, amygdala and hippocampus dysfunction, behavioral changes, panic disorder, suicidal ideation, schizophrenia, obsessive-compulsive symptomology, psychosis, irritability, impaired self-esteem, distorted body image
Cognitive	cognitive decrement, memory and concentration impairment, decreased attention span, forgetfulness
Quality of life	Residual deficit in physical and psychological scores