

Cushing's Syndrome in Children — Diagnosis and Treatment

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Cushing's syndrome is a rare disease in children and is a difficult condition to detect and manage. This article discusses the cause, presentation, and treatment of Cushing's syndrome in children.



Definition of Cushing's Syndrome

Cushing's syndrome is **also known as hypercortisolism**. It is a condition in which the body produces excess cortisol, due to the dysfunction of the pituitary gland, adrenal gland, or disturbance anywhere in the HPA (hypothalamic-pituitary-adrenal) axis.

Cushing's syndrome in children results in retarded growth, disrupted puberty, obesity, and various other signs and symptoms.

Introduction

Cushing syndrome is a **pathological culmination of chronic sustained exposure to escalated levels of glucocorticoids**. They can be endogenous or exogenous in origin. Cushing syndrome in children has a distinct identity from its adult counterpart.

The unique challenges incurred in the pediatric set up can be summarized as

follows:

- Reproductive function management
- Psychological health maintenance
- Body composition balance
- Bone mineral density affection
- Final height of the child
- Cosmetic appeal and appearance of the child



Image: "Physical examination revealed features of Cushing syndrome including round facies, acne, plethora, central obesity, and poor muscle tone." by Elizabeth B. Fudge, Daniel von Allmen, Keith E. Volmar and Ali S. Calikoglu. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

One needs to be aware of 2 closely related yet distinct terms when dealing with states of excess glucocorticoids circulating in the body. These are as follows:

Cushing's disease: When the source of excess ACTH leading to escalated levels of circulating glucocorticoids is a pituitary tumor, more specifically an ACTH-secreting **adenoma**, the patient concerned is said to have Cushing's disease.

Cushing's syndrome: This term epitomizes all the other manifestations of increased circulating glucocorticoids-both endogenously and exogenously derived.

History of Cushing's Syndrome in Children

Cushing syndrome was first described by **Harvey Cushing**, a voracious neurosurgeon in 1932. He was the one to expound the trans-sphenoidal surgery for pituitary adenomas and is rightfully known as the '**Father of Neurosurgery**'.

Epidemiology of Cushing's Syndrome in Children

Cushing's syndrome is rare in the pediatric population. It is observed in only 10% of the new cases per year. The most common age group afflicted is the young generation from 20-50 years. It is about three times more common in women than in men. But in pediatric cases, the opposite is true: it is more common in boys as compared to girls.

Etiology of Cushing's Syndrome in Children

The use of steroids in the medical management of certain illnesses is the predominant etiology in children. It is also called Iatrogenic Cushing's syndrome. The most relevant differences in pediatric Cushing's syndrome compared to the one encountered in adults can be summarized as follows:

- Early age Cushing's syndrome due to a predominance of mixed androgen and Cortisol-secreting adrenocortical tumors
- Cushing's syndrome in infancy caused due to McCune-Albright syndrome
- Increased frequency of prepubertal Cushing in boys rather than girls
- Seldom occurrence of ectopic ACTH syndrome
- Apparently increased difficulty in identifying the adenoma in pituitary scans
- Potentially increased tendency to detect lateralization of ACTH secretion on bilateral inferior petrosal sinus sampling (BIPSS)
- Relative early and improved response to external beam pituitary radiotherapy in the pediatric population

Etiopathogenesis of Cushing's Syndrome in Children

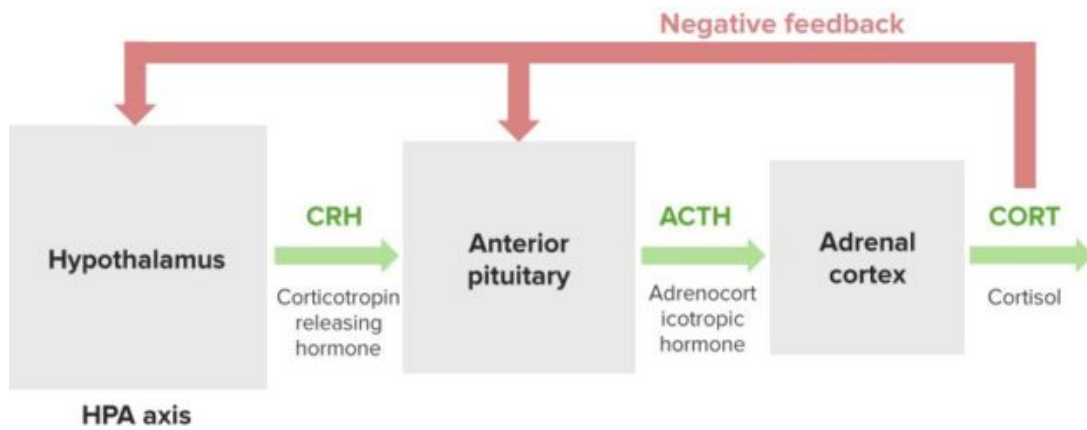
A prolonged state of overexposure to glucocorticoids results in Cushing's syndrome. This state of chaotic hormonal imbalance results from inappropriate control of the **Hypothalamic-pituitary-adrenal (HPA) axis**. A short description of the same is as follows:

HPA axis

The hypothalamus, anterior pituitary gland, and the adrenal glands are in a state of constant negative feedback. The normal functioning of this hypothalamic-pituitary-adrenal (HPA) axis is vital to the precise regulation of circulating glucocorticoids. The various components of the HPA axis and their origin can be summarized as follows:

Origin	Component
Hypothalamus	Corticotrophin-releasing hormone (CRH)
Anterior Pituitary	Adrenocorticotrophic hormone (ACTH)
Adrenal gland	Glucocorticoids such as Cortisol

CRH stimulates the release of ACTH which in turn downregulates the release of CRH through negative feedback. Cortisol exerts negative feedback and subsequent inhibition of release of both CRH and ACTH. Irrespective of the inciting factor, disruption of the normal immaculate functioning of this HPA axis results in Cushing's syndrome.



"The HPA Axis" Image created by Lecturio

Classification of Cushing's Syndrome in Children

Cushing's syndrome in children can be classified based on either etiology or as per the age of manifestation. Based on etiology, the classification is as follows:

ACTH-Dependent	ACTH-Independent
Pituitary adenoma (most common): Cushing's disease	Exogenous steroid
Ectopic ACTH syndrome (extremely rare)	Adrenocortical tumor (adenoma or carcinoma)
Carcinoid tumors: bronchial, renal, thymic or duodenal	Primary adrenocortical hyperplasia (associated with MEN syndrome-macronodular adrenal hyperplasia, McCune-Albright syndrome, PPAD, Carney complex)

Based on the age of onset, different subsets of Cushing's syndrome can be segregated as follows:

Age of onset	Feature
Infancy	Usually associated with McCune-Albright syndrome
Children under 4 years	Adrenocortical tumor is the most common etiology.
Children more than 5 years of age	Cushing's disease secondary to pituitary adenomas are most frequently encountered.

Few distinct syndromes associated with pediatric Cushing's syndrome need a mention.

McCune-Albright syndrome

Secondary to *GNAS1* gene mutation, this sporadic disease is an aggregation of characteristic features such as peripheral precocious puberty, polyostotic fibrous dysplasia, and cafe-au-lait pigmentation. Cushing's syndrome in infancy is most likely associated with this condition. It is an aggressive culmination of nodular adrenal hyperplasia.

Primary pigmented adrenocortical disease (PPAD)

This condition derives its name from the characteristic histological appearance of affected adrenal glands. Multiple pigmented adrenocortical nodules are seen, thus justifying the other name for this disease, 'micronodular adrenal disease'.

PPNAD has associated with Carney complex and Cushing's syndrome is the most common manifestation of Carney's complex in the pediatric population. Carney's complex comprises of cardiac myxomas, lentigines, and various endocrine and non-endocrine tumors.

Cyclical or periodic Cushing's syndrome

The patients with Carney's complex and PPNAD often have intermittent remissions thus leading to the concept of 'cyclical' Cushing's syndrome in these patients.

Atypical Cushing's syndrome

This term is uniquely expounded in relation to PPNAD. It is characterized by muscle and skin wasting, short stature, and osteoporosis.

Clinical Presentation of Cushing's Syndrome in Children

The patients with Cushing's syndrome in the pediatric population have typical, characteristic stark features and a distinct stereotype appearance, thus making Cushing's syndrome a potential clinical diagnosis. Subtle features are seldom seen. The most common characteristics are as follows:

Feature	Frequency
Fatigue	60 %
Hirsutism	60 %
Striae	51 %
Emotional lability	51 %
Hypertension	45 %

A detailed list of all significant Cushingoid signs and symptoms is summarized below for easy memorization and recall:

Sign	Symptom
<ul style="list-style-type: none"> • Moon facies • Violaceous striae • Plethora (redness) • Deregulated pubertal development <ul style="list-style-type: none"> • Short stature • Auxology: decrement in height SDS in association with increased BMI SDS • Buffalo hump (dorsocervical fat pad) <ul style="list-style-type: none"> • Myopathy • Lentigines (Carney complex) <ul style="list-style-type: none"> • Freckles • Virilization • Osteoporosis 	<ul style="list-style-type: none"> • Poor growth • Irritability • Fatigues <ul style="list-style-type: none"> • Acne • Headache • Emotional lability <ul style="list-style-type: none"> • Weight gain • Lethargy • Hirsutism • Easy bruisability • Family history

Diagnosis of Cushing's Syndrome in Children

Cushing's syndrome is potentially a clinical diagnosis. There are 2 tiers of investigations when it comes to pediatric Cushing's syndrome. The first is to reinstate the clinical diagnosis, and next to determine the etiology. The biochemical definition of Cushing's

syndrome is the disruption of the normal feedback mechanism of the HPA axis and deregulated circadian rhythm of glucocorticoid circulation and secretion. A combination of 2 or more tests typically yields high sensitivity and specificity.

Investigations thus relevant in Cushing's syndrome can be summarized as follows:

Investigation	Explanation
Urinary free Cortisol assessment	This highly sensitive test is the first one to be performed. Three consecutive 24-hour urine samples are collected and free Cortisol levels assessed.
Serum Cortisol measurement	Serum Cortisol levels fluctuate in accordance with the circadian rhythm. Midnight serum Cortisol more than 50nmol/L is one of the best discriminating tests.
Low dose Dexamethasone suppression test (LDDST)	In accordance with the NIH recommendations, 0.5 mg of Dexamethasone is administered every 6 hours for 24 hours in children less than 40 kg. For those over 40 kg, 30 ug/kg/day Dexamethasone is typically used. Serum Cortisol assessment is performed at 0, 24 and 48 hours. Cushing's syndrome is characterized by an inability to suppress Cortisol secretion secondary to loss of negative feedback mechanism. Consequently, one encounters increased Cortisol levels after 48 hours. 50 nmol/L is the typical cutoff used. LDDST plays a critical role in differentiating patients with Cushing's disease and Cushing's syndrome.
Midnight salivary Cortisol measurement	This screening test seems suitable for children because of its non-invasive nature.
Plasma ACTH level assessment	It is of crucial importance to differentiate ACTH-dependent Cushing's syndrome from ACTH-independent cases. Plasma ACTH levels are typically examined at about 0900 hours.
CRH (Corticotrophin-releasing hormone) test	CRH test is used selectively to differentiate Cushing's disease and ectopic ACTH secretion. The overwhelming response to CRH in the form of increased Cortisol levels by more than 20% is recorded in patients with Cushing's disease.
High-dose Dexamethasone suppression test (HDDST)	HDDST is falling out of favor recently. Dexamethasone is administered at a rate of 2 mg/6hrly (80 mcg/kg/d) for about 8 times in 48 hrs and then serum Cortisol level analysis is carried out.
Radiological investigations: CECT Abdomen SOS Chest MRI Adrenal MRI Brain-Pituitary protocol	CECT Abdomen is required in patients with adrenal etiology such as tumors and nodular hyperplasia. HRCT may be rarely required in cases such as carcinoid syndrome.
	Adrenal CT and MRI protocols help differentiate primary adrenal nodular hyperplasia and adrenocortical tumors.
	Pituitary microadenoma less than 5 mm is the frequent etiology of pediatric Cushing's syndrome. The same requires MRI Brain to locate the adenoma.
Genetic analysis	Genetic analysis is helpful in establishing the diagnosis of Carney's complex and associated PPAD. PRKAR1A gene mutations are assessed.
Bilateral Inferior Petrosal Sinus Sampling (BIPSS)	This investigation is used as a last resort to establish lateralization of ACTH secretion. It is an invasive test and not without complications.

Complications of Cushing's Syndrome in Children

The majority of complications are correlated with the direct or indirect effects of excessive glucocorticoids. Long-term exposure to cortisol leads to many complications and cardiovascular disease is the most important out of those. Cushing's syndrome is often associated with cardiovascular risk factors.

Some important complications are:

Hypertension: This may result from various disturbed mechanisms regulating plasma volume and peripheral vessel resistance or from direct cardiomyopathy due to the excessive levels of cortisol.

Impaired glucose tolerance/diabetes: Excessive glucocorticoids stimulate gluconeogenesis (glucose production) in the liver, along with the inhibition of insulin sensitivity, resulting in high levels of blood glucose.

Hyperlipidemia: High levels of cortisol result in exaggerated fat metabolism. Thus there is a rise in free fatty acids in the blood. There is also an increased synthesis of cholesterol and triglycerides resulting in total hyperlipidemia.

Hypokalemia: Cortisol is supposed to have some mineralocorticoid activity that results in the disturbance of potassium metabolism.

All these factors, in turn, predispose the patient to cardiovascular disease.

Management of Cushing's Syndrome in Children

The management of Cushing's syndrome in the pediatric population is apt in the hands of a multidisciplinary team. The etiology responsible determines the mode of the management applied. The multi-pronged attack often launched comprises of surgical, medical and radiological modalities of treatment. The same can be summarized as follows:

Surgical management

Surgical excision in the form of transsphenoidal surgery (TSS) microadenoma excision is the primary mode of treatment for Cushing's disease secondary to pituitary adenoma. Adrenalectomy is performed only if transsphenoidal surgery is impossible.

The management of PPAD and primary adrenal pathologies is often surgical. Optimum glucocorticoid replacement in the perioperative period is essential. Cure rates as high as 72% are achieved.

Medical management

Medical therapy is often used as a temporizing transit until the patient is optimized for surgical management. Adrenal blocking agents such as Metyrapone and Ketoconazole are frequently used. Mitotane is instrumental in the treatment of metastatic adrenocortical carcinoma.

Radiotherapy

It finds use in the treatment of Cushing's disease as a second-tier modality when transsphenoidal surgery fails to achieve remission. It is more successful in kids than in adults.

For patients with ectopic ACTH or suspected tumor, imaging and chemotherapy/surgical excision are necessary.

There are a few specific complications pertinent to transsphenoidal surgery for Cushing's disease in the pediatric population, which need a mention. The same can be tabulated as follows:

- Post-operative short stature, subnormal growth, and hypopituitarism
- Post-operative obesity
- Cognitive aberrations
- Psychological disturbances

The best treatment modality so far is not without complications. Hence, a multidisciplinary dedicated team comprising of pediatricians, surgeons and endocrinologists is vital to the management of Cushing's syndrome in the pediatric population.

Prognosis of Cushing's Syndrome in Children

- Untreated cases of Cushing's syndrome have a survival rate of 50% at 5 years.
- With therapy for cortisol normalization, the mortality rate is the same as the general population.
- Outcomes of surgery depend on the size of the tumor.

Summary

Secondary to chronic sustained abnormal exposure to increased glucocorticoids, Cushing's syndrome in the pediatric population is a rare diagnosis. The most common etiology is Cushing's disease secondary to an ACTH-secreting adenoma.

Children are not little people. The issues encountered in handling pediatric Cushing's syndrome are quite specific and need a dedicated multidisciplinary team for meticulous workup, management, and follow-up.

Cushing's syndrome is the ultimate culmination of the aberrant HPA axis and the loss of normal negative feedback.

The patients with Cushing's syndrome can be classified based on etiology or based on the stratification of etiology as per the age of the patient.

A few syndromic diseases associated with pediatric Cushing's syndrome are McCune-Albright syndrome and primary pigmented adrenocortical disease (PPNAD). Cushing's syndrome is the most common manifestation of Carney's complex in the pediatric population. The latter includes cardiac myxomas, lentigines, and complex endocrine and nonendocrine tumors.

Cushing's syndrome is a clinical diagnosis with stark characteristic signs and symptoms. Fatigue and hirsutism are most frequently encountered in the pediatric population.

Diagnosis is based on clinical suspicion further reinforced by several blood tests, which when used together supplement each other to ultimately yield high sensitivity and specificity.

Urinary cortisol level, low dose dexamethasone suppression test, ACTH level assessment and imaging studies as needed, commonly comprise the diagnostic armamentarium referred to for Cushing's syndrome. Other tests such as CRH measurement, high-dose Dexamethasone suppression test are seldom used.

The management of Cushing's syndrome is surgical, medical or based on the usage of radiotherapy as per the etiology. Transsphenoidal excision of pituitary adenoma is an established procedure for Cushing's disease. Hypopituitarism is a potential complication.

Medical therapy is often a temporizing solution before surgical management. Radiotherapy is typically reserved for patients with Cushing's disease who have failed transsphenoidal surgical management. Ultimately, it calls upon a dedicated multidisciplinary team to optimally manage Cushing's syndrome in pediatric patients.

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