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Neonatal Cushing Syndrome: A rare but potentially devastating disease

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Synopsis

Neonatal Cushing syndrome (CS) is most commonly caused by exogenous administration of glucocorticoids and rarely by endogenous hypercortisolemia. CS due to adrenal lesions is the most common cause of endogenous CS in neonates and infants, and adrenocortical tumors (ACTs) represent the majority of cases. Many of the ACTs develop in the context of a *TP53* gene mutation, which causes Li-Fraumeni syndrome. More rarely neonatal CS presents as part of other syndromes such as McCune–Albright syndrome (MAS) or Beckwith-Wiedemann syndrome (BWS). The management of the patients usually includes resection of the primary tumor with or without additional medical treatment, but manifestations may persist after resolution of hypercortisolemia.

Keynote words

Cushing syndrome; hypercortisolemia; Adrenocortical tumors; adrenal hyperplasia; infant

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Introduction

Cushing syndrome (CS) is named after Dr Harvey Cushing, an American neurosurgeon who first described the condition in a patient with weight gain, round face, hypertrichosis, muscle weakness, and irregular menstruations in 1912.¹ The term CS is currently used to describe the constellation of signs and symptoms that result from the chronic effects of hypercortisolemia.²

The etiology of CS is divided into exogenous (or iatrogenic) CS and endogenous [Adrenocorticotropin Hormone (ACTH)-dependent and ACTH-independent] CS. The widespread use of glucocorticoid (GC) treatment for various conditions (autoimmune, malignant, allergic) has rendered exogenous CS a common condition.^{3,4} The endogenous type is much more rare, with an estimated incidence of 2 to 5 new cases per million people diagnosed every year; of these only 10% refer to children. Endogenous neonatal CS remains extremely rare. Most of the cases present as part of an isolated adrenocortical tumor (ACT), commonly an adrenocortical carcinoma (ACC). Nearly 100 patients with neonatal and infantile CS not associated with isolated ACTs have been described until now (Supplemental Tables).⁵

CS is associated with significant clinical findings, such as hypertension, hyperglycemia, hyperlipidemia, decreased bone mineral density and muscular atrophy. More characteristically in children CS also leads to growth arrest, despite continuous weight gain.⁵ Given the severity of the various comorbidities, which may result in long term and irreversible complications, it is essential to recognize and appropriately manage CS as soon as possible.

The fetal and neonatal Hypothalamic-Pituitary-Adrenal (HPA) axis

The adrenal glands derive from the urogenital ridge of the intermediate mesoderm, which also differentiates into the gonads and the mesonephros.^{6,7} The development of the steroid producing cells starts at 4 weeks of gestation, and at 5 weeks the adrenal cells are clearly separated from the gonads.⁸ Around the same period (7 weeks of gestation), sympathetic nerve cells from the neural crest, migrate to the center of the adrenals to form the adrenal medulla.⁶ At 8 weeks of gestation, adrenals are distinct organs and the adrenal cortex consists of two separate zones, the fetal and the definitive zone.^{9,10}

The fetal zone comprises almost 80% of the adrenal gland volume at term and it is a hormonally active region. However, it has low levels of 3-beta hydroxysteroid dehydrogenase (HSD) and high levels of sulfotransferase enzyme concentrations, which renders dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) the main product of the fetal zone.¹¹ Those are further used by the placenta to maintain the estriol levels.¹²

The fetal zone starts to involute after birth and disappears by the end of the first year of life.¹⁰ The definitive zone, the outer zone that surrounds the fetal cortex, increases in size with age and it gives rise to the three known zones of the adult adrenal cortex (glomerulosa,

fasciculata, and reticularis) within the first 1–3 years of life, although its development is not completed until the puberty years.¹³

Cortisol has been detected as early as 8 weeks of gestation, and it has significant functions during the intrauterine life, including the lung, liver, thyroid and other organ maturation.¹⁴ The human fetal adrenal gland starts also secreting aldosterone, desoxycorticosterone (DOC), and corticosterone between 10 and 20 weeks.¹⁰ As mentioned above, DHEAS levels are high at birth but decline rapidly afterwards as the fetal zone involutes.¹⁰

The adrenal production of cortisol is under the control of the HPA axis. Corticotropin-releasing hormone (CRH) production has been reported in primates by the third trimester.¹⁵ However sources of CRH production outside the hypothalamus, such as the placenta, have also been documented to contribute significantly in the cortisol production during embryogenesis.¹⁶ The anterior lobe of the pituitary, where ACTH hormone is produced, derives from the oral ectoderm and it is fully formed by 5 weeks of gestation. Although ACTH is detected in the fetal pituitary by the 7th week of gestational age, its trophic properties become important for the maintenance of the fetal zone of the adrenals only after the first 4–5 months of gestation.⁹⁶ After birth, ACTH is the sole significant trophic factor of the definitive zone; however the fetal zone gradually involutes.

CRH is synthesized in the hypothalamus and carried to the anterior pituitary in the portal system; this may first happen after the second trimester in fetal life. CRH stimulates ACTH release from the anterior pituitary, which in turn stimulates the adrenal cortex to secrete cortisol.¹⁷¹⁸ Cortisol further inhibits the synthesis and secretion of both CRH and ACTH in a negative feedback regulation system (Figure 1). In children and adults (not prior to age 6 months), the hormones of the HPA axis follow a circadian rhythm of secretion. ACTH reaches a peak level between 06:00–09:00h, and a nadir level at 23:00–02:00h.¹⁹ Similarly, cortisol levels peak some time between 07:30 and 08:30h and then decrease with a nadir value at midnight.²⁰

The understanding of the physiology of the HPA axis is very important for the diagnostic workup of patients with CS, where autonomous secretion of ACTH and/or cortisol does not comply with the above rules.

Causes of Cushing Syndrome

1. Exogenous Cushing syndrome

The most commonly encountered cause of neonatal CS is the exogenous administration of pharmacologic doses of GCs, which comprises more than 95% of all cases. Although the report of the long-term complications of neonatal exposure to GCs (mainly metabolic and CNS related) has placed their perinatal use under consideration, GCs remain part of various therapeutic approaches, such as the management of fetal lung maturation prenatally, as well as respiratory, neurologic and other conditions postnatally.²¹²²²³²⁴ The effects of GCs on the suppression of the HPA is seen not only in systemic administration of the medications, but also in topically applied GCs.²⁵

2. Endogenous Cushing syndrome

The causes of endogenous CS are divided into ACTH-dependent and ACTH-independent (Table 1). Adrenal disorders cause ACTH-independent CS and they are the commonest cause of endogenous CS in neonates and infants. This category is very diverse, involving various adrenal diseases.

ACTs represent 0.2% of all pediatric tumors and they constitute the commonest cause of adrenal dependent CS in the first years of life.⁵²⁶ Although not all ACTs are associated with CS, signs of hypercortisolemia, isolated or in combination with hyperandrogenemia, have been identified in up to 50% of ACT cases.²⁷²⁸ Adrenocortical tumors are commonly malignant ACCs with poor prognosis (70% of cases), but they may also represent benign unilateral adrenocortical adenomas (ACAs).²⁷ ACTs present at a median age of 3–4 years old, but cases present even at birth have been previously described.²⁷²⁸

More rare benign bilateral adrenocortical hyperplasia may result in autonomous, ACTH-independent hypercortisolemia. This category is further divided according to the size of the nodules into macronodular (>1cm) and micronodular (<1cm) disease.²⁹³⁰ The micronodular adrenocortical nodular disease can be secondary to primary pigmented adrenocortical nodular disease (PPNAD) or non-pigmented isolated micronodular adrenocortical disease (iMAD). On the other hand, macronodular hyperplasia may present with multiple bilateral cortisol secreting nodules with internodular atrophy (bilateral macroadenomatous hyperplasia or BMAH) or without atrophy (massive macronodular adrenal hyperplasia or MMAD).²⁹³⁰

In older children and adults, ACTH-dependent CS results usually from pituitary corticotropin secreting adenomas (this is known as Cushing disease - CD).² The pituitary adenomas are commonly microadenomas (size <1cm) and more rare macroadenomas (size > 1cm) that exhibit a semiautonomous secretion of ACTH, which further leads to bilateral adrenal stimulation and cortisol production.³¹³² Although CD is the commonest cause of CS in older children, its prevalence is rare under the age of 7 years.⁵³³ Recently many of the previously reported infantile ACTH-secreting pituitary adenomas have been reclassified as pituitary blastomas.³⁴ These tumors are considered embryonal tumors, containing cells from all the stages of pituitary development as well as epithelial Rathke cells, which is a unique feature. In most of the reported cases, ACTH-dependent hypercortisolemia has been reported, but additional pituitary hormones might be oversecreted as well.³⁵

In rare occasions, ACTH-dependent CS may result from ectopic ACTH and/or CRH production, where the source of the ectopic hormone production is located in the lungs, the liver, the thymus, the pancreas or other neuroendocrine tumors.³⁶ In infancy specifically reports of ectopic ACTH production from neuroblastomas represent the majority of ectopic CS.³⁷

Genetic causes of neonatal and infantile Cushing Syndrome

Various genetic causes have been associated with the pathogenesis of adrenal CS, both in the adult and the pediatric population. *TP53* gene mutations are the most common cause of

adrenocortical tumors and are identified in almost 70% of ACTs.³⁸³⁹ This percentage is higher in pediatric patients with ACTs from Southern Brazil, where a point mutation of *TP53* gene (Arg337His) has been reported in 78 – 97% of cases.⁴⁰⁴¹ Germline *TP53* gene mutations may cause Li-Fraumeni syndrome (LFS) which is an autosomal dominant inherited syndrome predisposing to various cancers.⁴² Patients with LFS present with early onset (childhood) ACTs and increased risk for other malignancies (osteosarcoma, soft tissue sarcoma, breast cancer, brain tumors, leukemia and others).⁴³ The penetrance of the germline mutations is variable and it has been suggested that any child with ACT should be assessed for *TP53* mutations, irrespective of the family history.³⁹

Defects of various steps of the cyclic adenosine monophosphate - protein kinase A (cAMP/PKA) pathway have been also implicated in the pathogenesis of adrenal causes of CS.³³³⁸ McCune–Albright syndrome (MAS) presents with the clinical triad of bone fibrous dysplasia, café au-lait macules and precocious puberty. MAS results from postzygotic somatic mutations of the *GNAS* gene, which codes for the Gsa subunit of the G-protein coupled receptors, causing their constitutive activation which leads to elevated levels of the intracellular cAMP, irrespective of the ligand concentration.⁴⁴ Given the fact that many of the hormone receptors are G-coupled protein receptors, MAS may manifest as activating endocrinopathies of various types (hyperthyroidism, GH excess, precocious puberty and others).⁴⁴ The presence of CS in MAS has been described as early as in the neonate period and it is uncommon after the first year of life.⁴⁵ It presents as either unilateral adrenal nodules or bilateral adrenal hyperplasia.⁴⁶ The course of the disease is usually severe, even leading to death, but contrary to other CS cases, the patients who survive the acute phase of the disease without requiring adrenalectomy might experience spontaneous resolution.⁴⁵

Additional defects of the cAMP/PKA pathway include mutations in the *PRKARIA* gene, which codes for the regulatory subunit R1a of the PKA, and are the leading cause of Carney Complex (CNC).⁴⁷ CNC describes the association of myxomas, spotty skin pigmentation, endocrine overactivity, and psammomatous melanotic schwannomas. Up to 30% of CNC patients present with PPNAD some of them as children; however, no patient with PPNAD has ever been diagnosed with CS before the age of 1 year.⁴⁸ This may point to the different developmental origin of the adrenal lesions in PPNAD compared to other ACTs and MAS that present with CS in infancy.

Defects of the 11p15 locus involving *IGF2*, *H9* and *CDKI* genes, either in the somatic state in the adrenal tumors or identified as germline defects, as in patients with Beckwith-Wiedemann syndrome (BWS), have also been associated with the presence of adrenal dependent CS in the neonatal period.⁴⁹ BWS is a genetic overgrowth and cancer predisposition syndrome characterized by hemihypertrophy, macrosomia, macroglossia, organomegaly, hyperinsulinism, omphalocele/umbilical hernia, and distinct facial features.⁵⁰ Patients with BWS have an increased risk of developing intrabdominal tumors including hepatoblastomas, Wilm's tumors, rhabdomyosarcomas and ACTs, which are commonly identified early in life.⁵¹ Although most of the adrenocortical tumors are not resulting in CS, cases of hypercortisolemia have been reported in a few patients. CS in BWS may present as bilateral adrenal hyperplasia and it has been postulated to result from the delay of the maturation of the fetal adrenal gland.⁵² More recently an ACTH-secreting pituitary adenoma

has been reported in a 17yo patient with BWS and CD, however this is an infrequent presentation of the syndrome.⁵³

Other genetic defects that cause ACTs and CS, include *MEN1* gene mutations causing multiple endocrine neoplasia type 1 (MEN1), *APC* gene defects causing familial adenomatous polyposis (FAP), and others such as *SF1*, *PRKACA*, *PDE11A*, *PDE8B*, and *ARMC5* genetic changes. However, none of these conditions are known to cause CS in infancy, and they are very rarely the cause of hypercortisolemia before the age of 10 years.
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The genetic background of CD in children has been largely unknown until recently. Some of the known genes implicated in pituitary tumors, such as *MEN1*, *AIP*, *PRKAR1A*, *CDK1B*, and *CDKN2C*, explained only a small percentage of the pediatric cases.⁵⁶ Recently Reincke *et al* reported a high frequency of somatic mutations of the *USP8* gene, which has also been confirmed in 31% of pediatric CD.⁵⁷⁵⁸ However CD secondary to pituitary adenomas is extremely rare in infants.

On the contrary, pituitary blastomas represent the majority of the ACTH-dependent CS in infancy and most of these patients present with a germline or somatic *DICER1* gene mutation.³⁴ The *DICER1* protein is a small RNA processing endoribonuclease that cleaves precursor microRNAs (miRNA) into mature miRNAs. Germline mutations of the *DICER1* gene cause the pleuropulmonary blastoma familial tumor and dysplasia syndrome, which involves the presence of multiple benign and malignant tumors in addition to pituitary blastomas.⁵⁹

Clinical manifestations of Cushing Syndrome

The clinical presentation of CS can be rather insidious and initially the signs may easily be confused with other more common entities, such as obesity or constitutional delay of growth.³⁰ However as hypercortisolemia persists, the typical Cushinoid findings develop: central obesity, posterior neck fat deposition (buffalo hump), round facies, facial plethora, hirsutism, easy bruising, acne and decreased bone mineral density (Table 2, Figure 2).⁶⁰⁶¹⁶² Certain Cushing related manifestations, such as the violaceous striae, has been suggested to be less common in the infant population.⁵²⁷

In the growing infant and child specifically, one of the most important and earlier signs of isolated CS is the height deceleration along with continuous weight gain, which can be easily identified with review of the patient's growth chart.⁶³ Given however the high incidence of ACTs that co-secrete cortisol and androgens, an accelerated growth velocity has also been reported in 15–29% of these patients, and subsequently the absence of height deceleration cannot rule out the presence of hypercortisolemia. Furthermore, signs of hyperandrogenemia, including the presence of pubic hair, hypertrophy of the clitoris or the penis, acne and hirsutism, may sometimes be the presenting finding.²⁷²⁸

Hypercortisolemia may also induce suppression of the immune system and increased risk for severe and/or opportunistic infections. This is usually depicted on the abnormal white blood cell counts (leukocytosis, neutrophilia and lymphopenia), while clinical cases of severe

infections and even death secondary to cortisol induced immunosuppression have been reported.^{64,65} Additional findings that result from the hypercortisolemia include hypokalemia, hypercalcemia and hyperglycemia, while hyponatremia is less common.^{60,66} Hypertension is a finding of outmost significance in the pediatric CS population because it can be difficult to manage.⁶⁷ Patients with hypertensive complications such as seizures, intracerebral hemorrhage, and hypertensive crisis, leading even to death, have been previously described.^{27,68,69}

Diagnostic approach of Neonatal Cushing Syndrome

Although iatrogenic CS can easily be delineated by the review of the medical history of the patient and his previous and current medications, the diagnostic workup for endogenous CS involves various additional steps (Figure 3).

The establishment of the diagnosis of hypercortisolemia is usually based on three criteria: (1) the loss of the circadian rhythm of the cortisol secretion as documented with an elevated midnight serum or salivary cortisol level, (2) the elevation of the 24 h urine free cortisol (UFC) and (3) the lack of suppression of cortisol production after the administration of low dose overnight dexamethasone (1 mg or equivalent weight-based dose of 15mcg/kg in children). The presence of two abnormal test results strongly supports the diagnosis of CS.⁷⁰ The completion of the above tests can be complicated by the fact that the circadian rhythm of the neonates and infants does not necessarily follow the regular day/night rhythm of older children and adults. Circadian rhythms are just being established between 6 and 12 months of age. Additionally the 24 hour urine collection can be uncomfortable to obtain, since the presence of an indwelling catheter is usually necessary. Thus the interpretation of the above tests should be done in conjunction with the clinical presentation of the patient.

The biochemical evaluation should also include the measurement of the adrenal androgens in order to identify the cases of glucocorticoid and androgen co-secretion by adrenal tumors. DHEAS is the most specific adrenal hormone since the enzyme sulfatase that converts DHEA to DHEAS is found almost exclusively in the adrenals and 95% of the circulating DHEAS is coming from the adrenals. Additional hormones to be measured include androstenedione, testosterone and estradiol. Other markers of accelerated cell turnover, such as LDH, as well as tumor markers, such as AFP, CEA, and Ca125, should also be sent as part of the evaluation before the surgery and they can be used postoperatively for monitoring of recurrence.

After the establishment of the diagnosis of endogenous CS, ACTH levels should be measured to differentiate between ACTH-dependent (usually ACTH > 30 pg/ml) or ACTH-independent causes (suppressed ACTH < 5 pg/mL). In ACTH-dependent CS, MRI of the pituitary along with high dose dexamethasone suppression test (8mg or equivalent weight-based dose of 120 mcg/kg in children) and the CRH test are used to define the source of hypercortisolemia as either in the pituitary or ectopic. If those results are inconclusive, the bilateral inferior petrosal sinus sampling (BIPSS) could assist in defining the source of hypercortisolemia.²

In cases of ACTH-independent CS, imaging of the adrenals is the next diagnostic step in order to assess the presence of a unilateral tumor or bilateral adrenal disease. Ultrasound of the adrenals has not been proven to be sensitive in identifying adrenal masses beyond large ACTs and sizable carcinomas; thus, CT primarily (sensitive for small lesions less than 1 cm) or MRI (not as good for lesions less than 1 cm due to motion artifacts) are the recommended techniques. In the presence of bilateral adrenal disease or in cases of intermediate levels of ACTH, the standard 6-day low- and high-dose dexamethasone suppression test (Liddle's test) is used to differentiate between the various causes of CS. Calculation of the level of suppression of serum cortisol levels, and urinary free cortisol and 17-hydroxy steroids can lead towards a specific cause.²⁷¹

In more complicated cases, additional imaging studies, such as ¹⁸F-fluorodeoxyglucose (FDG) PET scan, octreotide scan or imaging studies of additional parts of the body may be indicated.⁷⁰

Management of Cushing Syndrome

The management of neonatal CS depends on the underlying cause of the disease. Although in the past the survival rate of neonates and infants diagnosed with CS was low (See Supplemental Tables), the advances of medicine have improved this over the last decades.

Adrenocortical carcinomas are managed with laparoscopic or open (depending on the size of the tumor and the suspicion of local invasion) complete en bloc resection of the primary tumor and the peritumoral/periadrenal retroperitoneal fat, and adjuvant chemotherapy with mitotane.⁷²⁷³⁷⁴ Benign adrenal tumors are usually managed with surgical resection with no need for additional treatment.

In cases of bilateral adrenal hyperplasia, patients are managed with bilateral adrenalectomy, which requires life-long glucocorticoid and mineralocorticoid replacement. Unilateral adrenalectomy or bilateral partial adrenalectomy has been also suggested as an alternative option, reserving the endogenous glucocorticoid production.⁷⁵ However in these cases regular monitoring for recurrence of CS should be undertaken. In CS associated with MAS specifically, given the possibility of spontaneous resolution of the disease, initial medical management or subtotal adrenalectomy could be attempted to preserve the adrenal function later in life.⁷⁶

Pituitary corticotropinomas are generally managed with transsphenoidal resection (TSS) with a high rate of success in specialized centers.⁷⁷⁷⁸ TSS approach however is difficult in young infants, given the limited space in the nostrils and the lack of pneumatization of the sphenoid sinus, which starts around the age of 2 years. Thus transcranial approach of the pituitary is usually required. Recently transsphenoidal approach has been successfully used even in young infants and provides an alternative less invasive technique.⁷⁹ Given the possibility of pituitary hormone deficiencies as a result of the manipulation of the pituitary gland and their long-term effects in the developing child, referral to a center with neurosurgeon specialized in pediatric tumors is highly recommended. In cases of persistent disease, repeat surgery may be considered, but the success rate is lower (60%) and the

possibility of persistent pituitary hormone deficiencies is higher.³⁸⁰ If hypercortisolemia persists, then radiation or medical treatment (ketoconazole, metyrapone, mitotane, mifepristone) are additional options to control the hypercortisolemia.⁸¹

Postoperatively the patients require glucocorticoid replacement with hydrocortisone until the recovery of the HPA is documented, which usually requires 12–18 months.⁸²

Documentation of recovery is based on a normal 8am serum cortisol level (> 6 mcg/dL) or a sufficient response of cortisol production (>18 mcg/dL) after administration of cosyntropin.⁸³

Despite the resolution of hypercortisolemia, patients with history of CS present with persistent features that need life long monitoring.⁷⁷ Those include persistent elevation of BMI, several risk factors for metabolic syndrome (hypertension, hyperlipidemia and impaired glucose tolerance), bone manifestations, and cognitive and psychological problems.⁷⁷

Summary

Neonatal CS is a rare condition in the neonate and infantile period. It is usually caused by an adrenal disease, most commonly adrenocortical tumor. Genetic causes explain a large portion of the patients, and the clinical presentation of the patient should guide appropriate genetic testing which is important for the prognosis and follow up evaluation. The diagnostic evaluation of CS should follow the recommended steps in order to distinguish ACTH-dependent from ACTH-independent etiologies and guide the appropriate management of the patient. Although surgical management of the source of hypercortisolemia may result in cure, long term manifestations of CS may persist and require regular monitoring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Lindholm J. Cushing's syndrome: historical aspects. *Pituitary*. 2000; 3(2):97–104. [PubMed: 11141701]
2. Stratakis CA. Diagnosis and Clinical Genetics of Cushing Syndrome in Pediatrics. *Endocrinology and metabolism clinics of North America*. 2016; 45(2):311–28. DOI: 10.1016/j.ecl.2016.01.006 [PubMed: 27241967]
3. Hench P. Effects of cortisone in the rheumatic diseases. *Lancet*. 1950; 2(6634):483–4. [PubMed: 14785191]
4. Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2006. *National health statistics reports*. 2008; (8):1–29.
5. Stratakis CA. Cushing syndrome in pediatrics. *Endocrinology and metabolism clinics of North America*. 2012; 41(4):793–803. DOI: 10.1016/j.ecl.2012.08.002 [PubMed: 23099271]
6. Villee DB. Development of endocrine function in the human placenta and fetus (first of two parts). *The New England journal of medicine*. 1969; 281(9):473–84. DOI: 10.1056/NEJM196908282810905 [PubMed: 4894430]
7. Ross IL, Louw GJ. Embryological and molecular development of the adrenal glands. *Clinical anatomy*. 2015; 28(2):235–42. DOI: 10.1002/ca.22422 [PubMed: 25255746]

8. Ferraz-de-Souza B, Achermann JC. Disorders of adrenal development. *Endocrine development*. 2008; 13:19–32. DOI: 10.1159/000134753 [PubMed: 18493131]
9. Buster JE. Fetal adrenal cortex. *Clinical obstetrics and gynecology*. 1980; 23(3):803–24. [PubMed: 6998629]
10. Seron-Ferre M, Jaffe RB. The fetal adrenal gland. *Annual review of physiology*. 1981; 43:141–62. DOI: 10.1146/annurev.ph.43.030181.001041
11. Melmed SPK, Larsen PR, Kronenberg HM. *Endocrinology of Fetal Development*. Williams Textbook of Endocrinology (12). 2011; Chapter 22:833–67.
12. Fisher DA. The unique endocrine milieu of the fetus. *The Journal of clinical investigation*. 1986; 78(3):603–11. DOI: 10.1172/JCI112616 [PubMed: 3018041]
13. Mesiano S, Jaffe RB. Developmental and functional biology of the primate fetal adrenal cortex. *Endocrine reviews*. 1997; 18(3):378–403. DOI: 10.1210/edrv.18.3.0304 [PubMed: 9183569]
14. Liggins GC. Adrenocortical-related maturational events in the fetus. *American journal of obstetrics and gynecology*. 1976; 126(7):931–41. [PubMed: 187057]
15. Dotzler SA, Digeronimo RJ, Yoder BA, et al. Distribution of corticotropin releasing hormone in the fetus, newborn, juvenile, and adult baboon. *Pediatr Res*. 2004; 55(1):120–5. DOI: 10.1203/01.PDR.0000100460.00639.F4 [PubMed: 14605257]
16. Goland RS, Wardlaw SL, Blum M, et al. Biologically active corticotropin-releasing hormone in maternal and fetal plasma during pregnancy. *American journal of obstetrics and gynecology*. 1988; 159(4):884–90. [PubMed: 2845784]
17. Tsigos C, Chrousos GP. Differential diagnosis and management of Cushing's syndrome. *Annu Rev Med*. 1996; 47:443–61. published Online First: 1996/01/01. DOI: 10.1146/annurev.med.47.1.443 [PubMed: 8712794]
18. Orth DN. Cushing's syndrome. *N Engl J Med*. 1995; 332(12):791–803. published Online First: 1995/03/23. DOI: 10.1056/NEJM199503233321207 [PubMed: 7862184]
19. Lim, CT., Grossman, A., Khoo, B. Normal Physiology of ACTH and GH Release in the Hypothalamus and Anterior Pituitary in Man. In: De Groot, LJ, Chrousos, G, Dungan, K., et al., editors. *Endotext*. South Dartmouth (MA): 2000.
20. Buckley TM, Schatzberg AF. On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. *The Journal of clinical endocrinology and metabolism*. 2005; 90(5):3106–14. DOI: 10.1210/jc.2004-1056 [PubMed: 15728214]
21. Seckl JR. Prenatal glucocorticoids and long-term programming. *European journal of endocrinology/European Federation of Endocrine Societies*. 2004; 151(Suppl 3):U49–62.
22. Baud O, Sola A. Corticosteroids in perinatal medicine: how to improve outcomes without affecting the developing brain? *Semin Fetal Neonatal Med*. 2007; 12(4):273–9. DOI: 10.1016/j.siny.2007.01.025 [PubMed: 17376752]
23. Rajadurai VS, Tan KH. The use and abuse of steroids in perinatal medicine. *Ann Acad Med Singapore*. 2003; 32(3):324–34. [PubMed: 12854376]
24. Onland W, De Jaegere AP, Offringa M, et al. Systemic corticosteroid regimens for prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database Syst Rev*. 2017; 1:CD010941.doi: 10.1002/14651858.CD010941.pub2 [PubMed: 28141913]
25. Ermis B, Ors R, Tastekin A, et al. Cushing's syndrome secondary to topical corticosteroids abuse. *Clin Endocrinol (Oxf)*. 2003; 58(6):795–6. [PubMed: 12780758]
26. Ribeiro RC, Pinto EM, Zambetti GP, et al. 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. DOI: 10.1016/j.mce.2011.10.015 [PubMed: 22040600]
27. Sandrini R, Ribeiro RC, DeLacerda L. Childhood adrenocortical tumors. *The Journal of clinical endocrinology and metabolism*. 1997; 82(7):2027–31. DOI: 10.1210/jcem.82.7.4057 [PubMed: 9215267]
28. Chen QL, Su Z, Li YH, et al. Clinical characteristics of adrenocortical tumors in children. *Journal of pediatric endocrinology & metabolism: JPEM*. 2011; 24(7–8):535–41. [PubMed: 21932594]

29. Stratakis CA, Boikos SA. Genetics of adrenal tumors associated with Cushing's syndrome: a new classification for bilateral adrenocortical hyperplasias. *Nat Clin Pract Endocrinol Metab.* 2007; 3(11):748–57. DOI: 10.1038/ncpendmet0648 [PubMed: 17955016]
30. Stratakis CA. Cushing syndrome caused by adrenocortical tumors and hyperplasias (corticotropin-independent Cushing syndrome). *Endocrine development.* 2008; 13:117–32. DOI: 10.1159/000134829 [PubMed: 18493137]
31. Gkourogianni A, Sinaii N, Jackson SH, et al. Pediatric Cushing disease: disparities in disease severity and outcomes in the Hispanic and African-American populations. *Pediatr Res.* 2017; doi: 10.1038/pr.2017.58
32. Libuit LG, Karageorgiadis AS, Sinaii N, et al. A gender-dependent analysis of Cushing's disease in childhood: pre- and postoperative follow-up. *Clin Endocrinol (Oxf).* 2015; 83(1):72–7. DOI: 10.1111/cen.12644 [PubMed: 25388128]
33. Lodish M, Stratakis CA. A genetic and molecular update on adrenocortical causes of Cushing syndrome. *Nat Rev Endocrinol.* 2016; 12(5):255–62. DOI: 10.1038/nrendo.2016.24 [PubMed: 26965378]
34. de Kock L, Sabbaghian N, Plourde F, et al. Pituitary blastoma: a pathognomonic feature of germ line DICER1 mutations. *Acta Neuropathol.* 2014; 128(1):111–22. DOI: 10.1007/s00401-014-1285-z [PubMed: 24839956]
35. Scheithauer BW, Horvath E, Abel TW, et al. Pituitary blastoma: a unique embryonal tumor. *Pituitary.* 2012; 15(3):365–73. DOI: 10.1007/s11102-011-0328-x [PubMed: 21805093]
36. Karageorgiadis AS, Papadakis GZ, Biro J, et al. Ectopic adrenocorticotrophic hormone and corticotropin-releasing hormone co-secreting tumors in children and adolescents causing Cushing syndrome: a diagnostic dilemma and how to solve it. *The Journal of clinical endocrinology and metabolism.* 2015; 100(1):141–8. DOI: 10.1210/jc.2014-2945 [PubMed: 25291050]
37. Espinas-Holder M, Defachelles AS, Weill J, et al. Paraneoplastic Cushing syndrome due to adrenal neuroblastoma. *Med Pediatr Oncol.* 2000; 34(3):231–3. [PubMed: 10696137]
38. Lodish M. Cushing's syndrome in childhood: update on genetics, treatment, and outcomes. *Current opinion in endocrinology, diabetes, and obesity.* 2015; 22(1):48–54. DOI: 10.1097/MED.000000000000127
39. Gonzalez KD, Noltner KA, Buzin CH, et al. Beyond Li Fraumeni Syndrome: clinical characteristics of families with p53 germline mutations. *J Clin Oncol.* 2009; 27(8):1250–6. DOI: 10.1200/JCO.2008.16.6959 [PubMed: 19204208]
40. Ribeiro RC, Sandrini F, Figueiredo B, et al. An inherited p53 mutation that contributes in a tissue-specific manner to pediatric adrenal cortical carcinoma. *Proc Natl Acad Sci U S A.* 2001; 98(16):9330–5. DOI: 10.1073/pnas.161479898 [PubMed: 11481490]
41. Latronico AC, Pinto EM, Domenice S, et al. An inherited mutation outside the highly conserved DNA-binding domain of the p53 tumor suppressor protein in children and adults with sporadic adrenocortical tumors. *The Journal of clinical endocrinology and metabolism.* 2001; 86(10):4970–3. DOI: 10.1210/jcem.86.10.7957 [PubMed: 11600572]
42. Li FP, Fraumeni JF Jr, Mulvihill JJ, et al. A cancer family syndrome in twenty-four kindreds. *Cancer Res.* 1988; 48(18):5358–62. [PubMed: 3409256]
43. Mai PL, Best AF, Peters JA, et al. Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer.* 2016; 122(23):3673–81. DOI: 10.1002/cncr.30248 [PubMed: 27496084]
44. Dumitrescu CE, Collins MT. McCune-Albright syndrome. *Orphanet J Rare Dis.* 2008; 3:12.doi: 10.1186/1750-1172-3-12 [PubMed: 18489744]
45. Brown RJ, Kelly MH, Collins MT. Cushing syndrome in the McCune-Albright syndrome. *The Journal of clinical endocrinology and metabolism.* 2010; 95(4):1508–15. DOI: 10.1210/jc.2009-2321 [PubMed: 20157193]
46. Carney JA, Young WF, Stratakis CA. Primary bimorphic adrenocortical disease: cause of hypercortisolism in McCune-Albright syndrome. *Am J Surg Pathol.* 2011; 35(9):1311–26. DOI: 10.1097/PAS.0b013e31821ec4ce [PubMed: 21836496]

47. Kirschner LS, Carney JA, Pack SD, et al. Mutations of the gene encoding the protein kinase A type I-alpha regulatory subunit in patients with the Carney complex. *Nature genetics*. 2000; 26(1):89–92. DOI: 10.1038/79238 [PubMed: 10973256]
48. Stratakis CA. Carney complex: A familial lentiginosis predisposing to a variety of tumors. *Rev Endocr Metab Disord*. 2016; 17(3):367–71. DOI: 10.1007/s11154-016-9400-1 [PubMed: 27943004]
49. Gicquel C, Bertagna X, Schneid H, et al. Rearrangements at the 11p15 locus and overexpression of insulin-like growth factor-II gene in sporadic adrenocortical tumors. *The Journal of clinical endocrinology and metabolism*. 1994; 78(6):1444–53. DOI: 10.1210/jcem.78.6.7911125 [PubMed: 7911125]
50. Shuman, C., Beckwith, JB., Weksberg, R. Beckwith-Wiedemann Syndrome. In: Pagon, RA. Adam, MP. Ardinger, HH., et al., editors. *GeneReviews(R)*. Seattle (WA): 1993.
51. MacFarland SP, Mostoufi-Moab S, Zelle K, et al. Management of adrenal masses in patients with Beckwith-Wiedemann syndrome. *Pediatr Blood Cancer*. 2017; 64(8)doi: 10.1002/pbc.26432
52. Carney JA, Ho J, Kitsuda K, et al. 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):1452–63. DOI: 10.1097/PAS.0b013e31825d538b [PubMed: 22982888]
53. Brioude F, Nicolas C, Marey I, et al. Hypercortisolism due to a Pituitary Adenoma Associated with Beckwith-Wiedemann Syndrome. *Horm Res Paediatr*. 2016; 86(3):206–11. DOI: 10.1159/000446435 [PubMed: 27255538]
54. Ribeiro RC, Pinto EM, Zambetti GP. Familial predisposition to adrenocortical tumors: clinical and biological features and management strategies. *Best Pract Res Clin Endocrinol Metab*. 2010; 24(3):477–90. DOI: 10.1016/j.beem.2010.03.002 [PubMed: 20833338]
55. Almeida MQ, Latronico AC. The molecular pathogenesis of childhood adrenocortical tumors. *Horm Metab Res*. 2007; 39(6):461–6. DOI: 10.1055/s-2007-981476 [PubMed: 17578765]
56. Stratakis CA, Tichomirowa MA, Boikos S, et al. The role of germline AIP, MEN1, PRKAR1A, CDKN1B and CDKN2C mutations in causing pituitary adenomas in a large cohort of children, adolescents, and patients with genetic syndromes. *Clinical genetics*. 2010; 78(5):457–63. DOI: 10.1111/j.1399-0004.2010.01406.x [PubMed: 20507346]
57. Reincke M, Sbiera S, Hayakawa A, et al. Mutations in the deubiquitinase gene USP8 cause Cushing's disease. *Nature genetics*. 2015; 47(1):31–8. DOI: 10.1038/ng.3166 [PubMed: 25485838]
58. Faucz FR, Tirosh A, Tatsi C, et al. Somatic USP8 gene mutations are a common cause of pediatric Cushing disease. *The Journal of clinical endocrinology and metabolism*. 2017; doi: 10.1210/jc.2017-00161
59. Foulkes WD, Priest JR, Duchaine TF. DICER1: mutations, microRNAs and mechanisms. *Nat Rev Cancer*. 2014; 14(10):662–72. DOI: 10.1038/nrc3802 [PubMed: 25176334]
60. Magiakou MA, Mastorakos G, Oldfield EH, et al. Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. *The New England journal of medicine*. 1994; 331(10):629–36. DOI: 10.1056/NEJM199409083311002 [PubMed: 8052272]
61. Stratakis CA, Mastorakos G, Mitsiades NS, et al. Skin manifestations of Cushing disease in children and adolescents before and after the resolution of hypercortisolemia. *Pediatric dermatology*. 1998; 15(4):253–8. [PubMed: 9720685]
62. Tack LJ, Tatsi C, Stratakis CA, et al. Effects of Glucocorticoids on Bone: What we can Learn from Pediatric Endogenous Cushing's Syndrome. *Horm Metab Res*. 2016; 48(11):764–70. DOI: 10.1055/s-0042-117721 [PubMed: 27728929]
63. Magiakou MA, Mastorakos G, Chrousos GP. Final stature in patients with endogenous Cushing's syndrome. *The Journal of clinical endocrinology and metabolism*. 1994; 79(4):1082–5. DOI: 10.1210/jcem.79.4.7962277 [PubMed: 7962277]
64. Oppong E, Cato AC. Effects of Glucocorticoids in the Immune System. *Advances in experimental medicine and biology*. 2015; 872:217–33. DOI: 10.1007/978-1-4939-2895-8_9 [PubMed: 26215996]

65. Gkourogianni A, Lodish MB, Zilbermint M, et al. Death in pediatric Cushing syndrome is uncommon but still occurs. *Eur J Pediatr*. 2015; 174(4):501–7. DOI: 10.1007/s00431-014-2427-y [PubMed: 25241829]
66. Scaroni C, Zilio M, Foti M, et al. Glucose Metabolism Abnormalities in Cushing Syndrome: From Molecular Basis to Clinical Management. *Endocrine reviews*. 2017; 38(3):189–219. DOI: 10.1210/er.2016-1105 [PubMed: 28368467]
67. Lodish MB, Sinaii N, Patronas N, et al. Blood pressure in pediatric patients with Cushing syndrome. *The Journal of clinical endocrinology and metabolism*. 2009; 94(6):2002–8. DOI: 10.1210/jc.2008-2694 [PubMed: 19293264]
68. Nguyen JH, Lodish MB, Patronas NJ, et al. Extensive and largely reversible ischemic cerebral infarctions in a prepubertal child with hypertension and Cushing disease. *The Journal of clinical endocrinology and metabolism*. 2009; 94(1):1–2. DOI: 10.1210/jc.2008-1346 [PubMed: 19126630]
69. Bartz SK, Karaviti LP, Brandt ML, et al. Residual manifestations of hypercortisolemia following surgical treatment in a patient with Cushing syndrome. *Int J Pediatr Endocrinol*. 2015; 2015(1):19. doi: 10.1186/s13633-015-0014-2 [PubMed: 26322079]
70. Lacroix A, Feelders RA, Stratakis CA, et al. Cushing's syndrome. *Lancet*. 2015; 386(9996):913–27. DOI: 10.1016/S0140-6736(14)61375-1 [PubMed: 26004339]
71. Stratakis CA, Sarlis N, Kirschner LS, et al. Paradoxical response to dexamethasone in the diagnosis of primary pigmented nodular adrenocortical disease. *Ann Intern Med*. 1999; 131(8):585–91. [PubMed: 10523219]
72. Berruti A, Baudin E, Gelderblom H, et al. Adrenal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012; 23(Suppl 7):vii131–8. DOI: 10.1093/annonc/mds231 [PubMed: 22997446]
73. Gaujoux S, Mihai R, et al. joint working group of E. European Society of Endocrine Surgeons (ESES) and European Network for the Study of Adrenal Tumours (ENSAT) recommendations for the surgical management of adrenocortical carcinoma. *Br J Surg*. 2017; 104(4):358–76. DOI: 10.1002/bjs.10414 [PubMed: 28199015]
74. Berruti A, Grisanti S, Pulzer A, et al. Long-Term Outcomes of Adjuvant Mitotane Therapy in Patients With Radically Resected Adrenocortical Carcinoma. *The Journal of clinical endocrinology and metabolism*. 2017; 102(4):1358–65. DOI: 10.1210/jc.2016-2894 [PubMed: 28324035]
75. Lowery AJ, Seeliger B, Alesina PF, et al. Posterior retroperitoneoscopic adrenal surgery for clinical and subclinical Cushing's syndrome in patients with bilateral adrenal disease. *Langenbecks Arch Surg*. 2017; doi: 10.1007/s00423-017-1569-6
76. Itonaga T, Goto H, Toujigamori M, et al. Three-Quarters Adrenalectomy for Infantile-Onset Cushing Syndrome due to Bilateral Adrenal Hyperplasia in McCune-Albright Syndrome. *Horm Res Paediatr*. 2017; doi: 10.1159/000473878
77. Keil MF. Quality of life and other outcomes in children treated for Cushing syndrome. *The Journal of clinical endocrinology and metabolism*. 2013; 98(7):2667–78. DOI: 10.1210/jc.2013-1123 [PubMed: 23640970]
78. Chandler WF, Barkan AL, Hollon T, et al. Outcome of Transsphenoidal Surgery for Cushing Disease: A Single-Center Experience Over 32 Years. *Neurosurgery*. 2016; 78(2):216–23. DOI: 10.1227/NEU.0000000000001011 [PubMed: 26348007]
79. Zaben M, Zafar M, Bukhari S, et al. Endoscopic transsphenoidal approach for resection of malignant pituitary blastoma in an 18-month-old infant: a technical note. *Neurosurgery*. 2014; 10(Suppl 4):649–53. DOI: 10.1227/NEU.0000000000000474 [PubMed: 24978649]
80. Lonser RR, Wind JJ, Nieman LK, et al. Outcome of surgical treatment of 200 children with Cushing's disease. *The Journal of clinical endocrinology and metabolism*. 2013; 98(3):892–901. DOI: 10.1210/jc.2012-3604 [PubMed: 23372173]
81. Feelders RA, Hofland LJ. Medical treatment of Cushing's disease. *The Journal of clinical endocrinology and metabolism*. 2013; 98(2):425–38. DOI: 10.1210/jc.2012-3126 [PubMed: 23345100]

82. Lodish M, Dunn SV, Sinaii N, et al. Recovery of the hypothalamic-pituitary-adrenal axis in children and adolescents after surgical cure of Cushing's disease. *The Journal of clinical endocrinology and metabolism*. 2012; 97(5):1483–91. DOI: 10.1210/jc.2011-2325 [PubMed: 22399509]
83. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. *The Journal of clinical endocrinology and metabolism*. 2016; 101(2):364–89. DOI: 10.1210/jc.2015-1710 [PubMed: 26760044]

Key points

- Neonatal Cushing Syndrome (CS) is a rare disorder, but it can lead to significant complications and even death, if not diagnosed and treated promptly.
- Adrenocortical tumors (ACTs) are the most common cause of neonatal CS and they usually represent adrenocortical carcinomas (ACCs).
- Neonatal CS may present as part of a genetic syndrome, such as Li-Fraumeni syndrome (LFS), McCune-Albright syndrome (MAS), Beckwith-Wiedemann syndrome (BWS), and DICER1 mutations.
- The diagnosis of CS includes the documentation of loss of the circadian rhythm of cortisol production, elevation of urine free cortisol (UFC) and lack of suppression of cortisol production after dexamethasone administration.
- Surgical resection of the adrenal tumor is the current approach of treatment for ACTs. Adjuvant chemotherapy should be considered in cases of ACCs.

Best Practices Box**What is the current practice?**

- Cushing syndrome is suspected on the basis of the patient's clinical presentation (see Table 2).
- Confirmation of hypercortisolemia requires at least two abnormal results in the screening tests:
 1. Abnormal circadian rhythm of cortisol secretion (may not be definitive at age < 1 year)
 2. Elevated urine free cortisol levels and
 3. Lack of suppression of cortisol production after dexamethasone administration.
- After confirmation of hypercortisolemia, further evaluation of the source is suggested according to the diagnostic algorithm in Figure 3.

Figure 1.
Illustration of the HPA axis.

Figure 2. Picture of patient with neonatal Cushing syndrome and MAS. Note the round cushinoid face, the body obesity, the hypertrichosis of the face (A) and the characteristic café-au-lait macules on the abdomen (B).

Figure 3.
Diagnostic approach of Cushing syndrome

Table 1

Causes of Neonatal Cushing syndrome

Cause	Mechanism
Exogenous	Iatrogenic administration of pharmacologic doses of GCs
ACTH-Dependent CS	Pituitary ACTH secreting adenoma (Cushing Disease)
	Ectopic ACTH and/or CRH secretion
	Pituitary blastoma
ACTH-Independent CS	Adrenocortical carcinoma
	Adrenocortical adenoma
	Bilateral adrenocortical hyperplasia disease
	Micronodular (size of nodules < 1cm) <ul style="list-style-type: none"> • Primary Pigmented Adrenocortical Nodular Disease (PPNAD) • Isolated Micronodular Adrenocortical Disease (iMAD)
	Macronodular (size of nodules > 1cm) <ul style="list-style-type: none"> • Bilateral Macroadenomatous Hyperplasia (BMAH) • Massive Macronodular Adrenal Hyperplasia (MMAD)

Table 2

Manifestations of Neonatal Cushing syndrome

System	Finding
Growth	Obesity/Weight gain
	Height deceleration
Skin	Easy bruising
	Striae
	Hirsutism
	Acne
	Dorsal fat pad
	Facial plethora
	Acanthosis nigricans
Cardiovascular	Hypertension
Musculoskeletal	Osteopenia and increased fracture risk
	Proximal muscle weakness
Immunologic	Lymphopenia
	Increased risk for infections
Neurocognitive	Sleep disorders
	Anxiety
	Depression
Abnormal laboratory	Hyperglycemia
	Hypokalemia
	Hyperlipidemia