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Adrenal Dysfunction

Phyllis W Speiser*

Division of Pediatric Endocrinology, Cohen Children's Medical Center of New York, School of Medicine, Hofstra-North Shore LIJ, USA

Abstract

Adrenal cortical disease, especially adrenal insufficiency, is more common than adrenal medullary disease and often goes unrecognized for extended periods. Physicians should consider the diagnosis of adrenal insufficiency in any patient with non-specific unexplained signs or symptoms including hypoglycemia, growth failure, weight loss, vomiting, or lethargy. The clinical features may be mistaken for, and should be differentiated from, infection, malnutrition, and gastrointestinal disease, inborn errors of metabolism, anorexia, chronic fatigue syndrome, and depression.

Keywords: Adrenal dysfunction; malnutrition; hypoglycemia; anorexia

Anatomy and Physiology

The adrenal glands each weigh about 4 grams in full-term infants at birth, which is equivalent to that of adult glands; however, adrenal size decreases by about 50% to 60% within the first week of life and then enlarges in mid-childhood at the time of adrenarche. There is an inner medulla and an outer cortex, linked by vascular supply and hormonal influence. Within the mature adrenal cortex are 3 functionally distinct zones: the glomerulosa, comprising about 15% of the gland; fasciculata, the largest zone, comprising about 75% of the gland; and the reticularis, comprising about 10% of the gland.

The adrenal medulla is regulated by the sympathetic nervous system and secretes catecholamines, while the 3 zones of the cortex secrete steroid hormones categorized, respectively, as mineralocorticoids, glucocorticoids, and sex steroids. Mineralocorticoid production, exemplified by aldosterone, is principally regulated by the renin-angiotensin axis and by ambient potassium levels. Mineralocorticoids govern sodium and potassium homeostasis, and deficiencies in their production or action cause hyponatremia, hyperkalemia, and dehydration. Glucocorticoid and adrenal sex steroid production are primarily regulated by pituitary corticotrophin (ACTH) and hypothalamic corticotrophin-releasing hormone, secreted mainly in the early morning hours (0400 to 0800 hours) or in response to stress. Cortisol is the main glucocorticoid, and De-hydro-epi-androsterone (DHEA) is the main adrenal sex hormone. The latter is only a weak androgen, but it may be converted via androstenedione to either estrogens or androgens. The placenta utilizes fetal adrenal DHEA to produce estrogens, especially estriol, a marker hormone of fetal viability. Rising levels of DHEA and its sulfate later in childhood signal adrenarche, which usually precedes the development of body hair and apocrine odor at puberty [1].

Glucocorticoids promote protein and lipid breakdown and inhibit protein synthesis. The effects of cortisol counter-regulate those of insulin, increasing the concentration of glucose by stimulating gluconeogenesis and by decreasing glucose utilization in muscle. The net effect is increased production and conservation of glucose for use by essential tissues, such as the brain and red blood cells, at the expense of less essential tissues during times of stress or starvation. Clinicians should be aware that therapeutic doses of glucocorticoids are almost always supraphysiologic, and may suppress growth by antagonizing the production and action of Growth Hormones (GHs). Susceptibility to these effects is quite variable, and may be based in part on polymorphism in the glucocorticoid receptors [2].

Cortisol contributes to the maintenance of normal blood pressure through several mechanisms, notably increasing vascular sensitivity to pressors. At high concentrations, cortisol acts as a mineralocorticoid agonist, causing sodium and water retention. Cortisol and/or aldosterone deficiencies often result in shock if unrecognized and untreated [3].

Adrenal Insufficiency

History and physical examination

The symptoms of cortisol deficiency include lethargy, fatigue, weakness, dizziness, and anorexia. Signs detected at physical examination include hyperpigmentation, orthostatic hypotension, tachycardia, and weight loss. These findings are nonspecific and gradual in onset, and they may be mistaken for infection, malnutrition, and gastrointestinal disease, inborn errors of metabolism, anorexia, chronic fatigue syndrome, and depression. In some patients, gastrointestinal symptoms such as abdominal cramps, nausea, vomiting, and diarrhea are prominent. In adolescents and adults, sexual and/or reproductive dysfunction with decreased libido, potency, or amenorrhea may accompany either primary or secondary adrenal insufficiency. Orthostatic hypotension is more marked in primary than secondary adrenal insufficiency. This is because primary adrenal insufficiency is often associated with a combination of cortisol, aldosterone, and in some cases catecholamine, deficiencies.

Patients with chronic primary adrenal insufficiency often have hyperpigmentation of the non-sun-exposed skin and mucosal surfaces. This is the result of high plasma corticotrophin (ACTH) and accompanying Melanocyte-Stimulating Hormone (MSH) secretion due to absent cortisol feedback. Skin pigment changes may be difficult to appreciate in dark-skinned individuals. In contrast, patients with secondary adrenal insufficiency tend to be pale. Another symptom of primary adrenal insufficiency is a craving for salt, which is a result of aldosterone deficiency and resultant sodium wasting. Weight loss and failure to thrive may also be observed. Loss of axillary and/or pubic hair is common among hypoadrenal patients, who have low levels of adrenal androgens.

***Corresponding author:** Phyllis W Speiser, Division of Pediatric Endocrinology, Cohen Children's Medical Center of New York, School of Medicine, Hofstra-North Shore LIJ, 1991 Marcus Avenue, Suite M100, Lake Success, NY, USA, Tel: 516-472-3750/3755; Fax: 516-472-3751; E-mail: pspeiser@NSHS.edu

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Basic laboratory evaluation

The most commonly recognized screening laboratory findings are hypoglycemia and low early morning plasma cortisol. Such patients should be referred to an endocrinologist for further evaluation.

Children with secondary adrenal insufficiency might have delayed growth and puberty, manifestations of multiple anterior pituitary hormone deficiencies including GH, and gonadotropin deficiencies in addition to ACTH deficiency. Polyuria and polydipsia indicative of diabetes insipidus may also be seen in pituitary disorders affecting the neurohypophysis. Chronic unexplained signs or symptoms such as those described above should prompt endocrine consultation to determine whether further testing is required. Patients in hypotensive crisis or shock at the time they seek care should be treated urgently in the office or transferred immediately by ambulance to the nearest emergency center.

Pathology

Primary adrenal disease may be associated with either glandular hypoplasia or hyperplasia. The most common forms of adrenal pathology involve either deficient or excessive cortisol production. Table 1 lists various causes of adrenal insufficiency. Only the most commonly encountered disorders will be reviewed in detail in this chapter. Online Mendelian Inheritance in Man (OMIM) should be consulted for a more detailed discussion of rarer diseases; OMIM catalog numbers for each adrenal disease are listed in Table 1.

Causes primary of adrenal failure

Congenital Adrenal Hyperplasia (CAH) is the most common inborn error in adrenal function and the most common cause of adrenal insufficiency in the pediatric age group. It is most often caused by deficiency of steroid 21-hydroxylase [4]. In classic severe salt-wasting CAH, both cortisol and aldosterone production are impaired while adrenal androgen production is excessive. As a result of the lack of the vital hormones cortisol and aldosterone, patients are susceptible to potentially lethal adrenal insufficiency if untreated; this is also true of other forms of CAH that interrupt synthesis of these hormones (e.g. the rarer 3β - hydroxysteroid dehydrogenase deficiency and cholesterol desmolase deficiency). Excess androgen production, a side effect of 21-hydroxylase deficiency, causes genital ambiguity in newborn girls. In contrast, however, boys affected with severe 21-hydroxylase deficiency have no overt genital anomalies. To prevent mortality from adrenal crisis, among other reasons, the United States and many other countries perform newborn screening for this disease. Prompt treatment with glucocorticoids and mineralocorticoids is life-saving. About a quarter of patients with classic CAH produce enough aldosterone to avoid salt-wasting crises, and are termed "simple virilizers."

A milder, nonclassic form of CAH not associated with genital ambiguity or adrenal insufficiency may be missed by newborn screening programs. Because nonclassic CAH is characterized by less marked adrenal androgen excess, symptoms and signs do not often develop before middle childhood. These often include early pubic hair and/or rapid advances in height in both sexes. In many cases, these individuals either go undetected, or are diagnosed in adolescent girls or women with hirsutism, oligomenorrhea, or acne. The mild form of CAH may be mistaken in girls for polycystic ovarian syndrome [5].

Not all persons with nonclassic 21-hydroxylase deficiency are symptomatic. Boys in particular are much less likely to be troubled by this mild adrenal hormone imbalance. Even some girls and women remain asymptomatic. Thus, in the absence of rapidly advancingprecocious pubarche or other symptoms of androgen excess treatment may not be needed.

Laboratory Evaluation of CAH

The diagnosis of CAH rests on both the clinical manifestations and on specific hormone measurements. The gold standard test is a corticotropin-stimulated serum 17-hydroxyprogesterone, although analysis of serum levels of this hormone taken before 0800 hours may also be diagnostic. This is true because of the natural circadian pattern of endogenous ACTH secretion, which is highest between 0400 and 0800. It is important to measure adrenal hormones by the method of tandem mass spectrometry in an endocrine specialty laboratory that employs strict quality-control standards to avoid false-positive high levels generated by other nonspecific assays that capture cross-reacting hormones.

Genetics of CAH

Phenotypic variability among classic and nonclassic forms of CAH is attributable to allelic variation in the gene encoding active steroid 21-hydroxylase, CYP21A2. The disease is inherited as an autosomal recessive trait. There are >150 known disease-causing mutations, but approximately 10 mutations comprise about 90% of disease alleles in most populations. The spectrum of disease ranges from severe to mild, depending on which CYP21A2 mutations a patient carries. Genotyping can be useful in verifying an equivocal hormonal diagnosis; it is particularly valuable in prenatal diagnosis and genetic counseling [6].

Management and Long-Term Follow-up of CAH

CAH is treatable with oral corticosteroid medications. In its classical form, CAH requires lifelong medical management. Salt-wasting patients require both glucocorticoids and mineralocorticoids in early life. However, increasing dietary salt consumption may permit mineralocorticoids to be tapered and in some cases discontinued. Infants who consume very little dietary sodium, patients in tropical climates, or those who engage in intense exercise with excessive sweat sodium losses may require supplemental sodium chloride. Poorly controlled simple virilizing patients also benefit from mineralocorticoid therapy because it spares the use of high-dose glucocorticoids in some cases. Symptomatic nonclassic patients require low-dose glucocorticoids therapy only [6]. The preferred drugs are hydrocortisone for its lower potential for adverse side effects and fludrocortisone as the only available oral mineralocorticoid. Table 2 lists approximate relative glucocorticoids potencies.

Dosing should be titrated to maintain the levels of adrenal androgen precursors in the normal to mildly increased range. One should assay 17-hydroxyprogesterone, androstenedione, and testosterone; plasma renin activity is added to this profile in patients requiring mineralocorticoid replacement. Blood pressure should be monitored regularly in all patients. Attempts to suppress 17-hydroxyprogesterone to the normal range usually require excessively high glucocorticoids doses and have the undesirable consequence of growth suppression and iatrogenic Cushing syndrome. Measurement of ACTH is not helpful; this hormone seldom is completely suppressible in treated CAH patients. It is important to recognize that testosterone is not as useful a hormonal marker of adequate therapy in adolescent boys and men, although it is helpful in managing pre-pubertal children of sexes, as well as adolescent girls and women.

Other aspects of CAH treatment include ensuring that adolescent females with severe forms of CAH undergo gynecologic examination in anticipation of sexual activity; vaginoplasty may be necessary,

depending on whether and which genital surgical procedures were performed in the past [7]. Psychological counseling should be provided to these young women by a professional experienced in treating this type of disorder [8].

Adolescent boys should undergo careful testicular palpation and sonography to exclude testicular adrenal rests that can compromise fertility. Strict control of adrenal hormone levels can shrink such benign tumors in many cases [9].

Other Causes of Adrenal Failure

Primary adrenal insufficiency is estimated to affect about 100 per million people [10]. The syndrome, originally described by English physician Thomas Addison, included wasting, hyperpigmentation, and adrenal gland atrophy. In adults, over 80% of cases are caused by autoimmune adrenal destruction, which is most prevalent in women aged 25 to 45 years but observed in both sexes at any age. The female-to-male ratio is about 3:1. Autoimmune adrenalitis may be isolated or found in association with other autoimmune syndromes. Autoimmune Poly-endocrine Syndrome 1 (APECED due to defects in the AIRE autoimmune regulator gene) is associated with autoimmune poly-endocrinopathy, candidiasis, and ectodermal dystrophy. Addison disease and autoimmune hypo-parathyroidism may be accompanied by autoimmune pernicious anemia, hepatitis, thyroiditis, and diabetes. The age at onset and severity of each of these problems is variable. Autoimmune polyendocrine syndrome 2, also termed Schmidt syndrome, is associated with Addison disease, autoimmune thyroiditis, and diabetes; no specific gene defect has been identified to date. Table 1 lists other rare diseases associated with adrenal insufficiency.

Adrenal infiltration by tuberculosis is the second most common cause worldwide. HIV infection is another potential infectious cause of adrenalitis [10]; both of these infections tend to cause insidious progression to hypoadrenalism. In contrast, catastrophic adrenal hemorrhage during overwhelming bacterial sepsis causes the abrupt onset of adrenal failure, from which patients may eventually recover [11].

Perhaps because of its rarity in children and adolescents, or due to the nonspecific symptoms, the diagnosis of adrenal insufficiency is frequently delayed or missed. If unrecognized, adrenal insufficiency may present as a life-threatening crisis with acute cardiovascular collapse.

Further Laboratory Evaluation of Adrenal Cortical Insufficiency

Primary adrenal insufficiency can be detected on the basis of low early-morning (0800 hours) cortisol accompanied by increased ACTH. If zona glomerulosa function is affected, hyponatremia and hyperkalemia will be accompanied by a high plasma renin activity and low serum aldosterone. In adrenal insufficiency due to pituitary or hypothalamic dysfunction, ACTH levels will be inappropriately low in comparison with a low cortisol measurement. The diagnosis can be confirmed by absence of at least a 2-fold increment in serum cortisol 60 minutes after stimulation with a standard dose of intravenous cosyntropin (ACTH 1–24). A low dose of cosyntropin can be used to test ACTH reserve in cases of suspected secondary adrenal insufficiency. The threshold for a normal cortisol response is variably 16-18 mcg/dl [10].

Imaging Studies

If adrenal hemorrhage is suspected, this can be detected by ultrasonography or Computed Tomographic (CT) scan.

Management

Once the diagnosis of adrenal insufficiency is established, continuing reminders to patients, families, and medical personnel regarding the need for higher doses of glucocorticoid replacement therapy during inter-current illnesses and surgery are required. Failure to increase glucocorticoid supplementation during physical stress remains a significant cause of morbidity and mortality in these patients. Patients should be given letters explaining their condition and appropriate emergency management. Sample letters may be found at the Web sites of the National Adrenal Diseases Foundation: http://www.nadf.us/tools/Addison's_Disease_Alert_Flyer.pdf for patients with Addison disease and the Congenital Adrenal Hyperplasia Research Education & Support Foundation http://www.caresfoundation.org/dosing/illness-and-emergency/ for patients with CAH. The latter website provides a link to an instructional video on emergency intramuscular hydrocortisone injection.

Secondary Adrenal Insufficiency

Secondary adrenal insufficiency is more common than primary adrenal insufficiency. The estimated prevalence is 150 to 280 per million people [12]. Abrupt discontinuation of glucocorticoid therapy exacerbated by stress is the most frequent cause of secondary adrenal insufficiency. This results from the widespread chronic treatment of inflammatory and neoplastic conditions with glucocorticoids. Acute hypoglycemia as a symptom of adrenal insufficiency has even been reported after the use of inhaled glucocorticoids [13]. It is important to recognize that normal statural growth does not preclude adrenal suppression while being treated with inhaled glucocorticoids [14].

Administration of steroids orally, intramuscularly, intranasally, inhaled, transdermally, or intraorbitally may result in suppression of the hypothalamic-pituitary-adrenal axis. As little as 2 weeks of high-dose glucocorticoid treatment may result in suppression of endogenous cortisol production for up to a year [15]. In children being treated for leukemia, a 4-week course of glucocorticoids has been shown to suppress the hypothalamic-pituitary axis for up to 8 weeks after discontinuation [16]. Suppression of the axis cannot reliably be predicted by either the dose or the duration of therapy [17].

Laboratory Evaluation of Secondary Adrenal Insufficiency

Documentation of an intact hypothalamic-pituitary-adrenal axis should be obtained before subjecting a patient to surgery if he has a known history of glucocorticoid treatment. This may be done by documenting plasma cortisol level taken at 0800 hours of more than 10 μg/dL, or by performing a cosyntropin (ACTH 1–24) challenge test and observing blood cortisol levels above 15 μg/dL after 30 to 60 minutes. Another robust test of ACTH reserve is insulin-induced hypoglycemia; however, many clinicians are reluctant to use the latter test because of the danger of potential hypoglycemic seizures. If such documentation cannot be obtained in time, it is safest to treat patients with supplemental stress corticosteroid coverage in the peri-operative period within 1 year of withdrawal of therapy [18].

Most secondary adrenal insufficiency that is unrelated to withdrawal of glucocorticoid therapy occurs in association with other pituitary hormone deficiencies. Panhypopituitarism, or deficiency of 2 or more pituitary hormones, may be either congenital or acquired. Anatomic abnormalities in the pituitary or stalk may be detected on Magnetic Resonance Imaging (MRI). A history of head trauma or cranial surgery should raise suspicion of potential pituitary dysfunction [19]. Aside from these causes of secondary adrenal in-sufficiency, there are several other rare syndromes. These include ACTH resistance associated with

Primary disorders associated with adrenal gland hyperplasia
• 21-Hydroxylase deficiency (gene CYP21A2, OMIM 210910)
• 3β-Hydroxysteroid dehydrogenase deficiency (gene HSD3B2, OMIM 201810)
• Cholesterol desmolase deficiency (gene CYP11A, OMIM 201710, 118485)
• Lipoid hyperplasia (gene STAR, OMIM 201710)
• Glucocorticoid resistance (gene GCCR, OMIM 138040)
• Wolman disease (gene LIPA, OMIM 278000)
Disorders associated with adrenal gland hypoplasia
• Adrenal hypoplasia congenita (gene NR0B1(DAX-1), OMIM 300200)
• Adrenocortical insufficiency with or without ovarian defect (gene NR5A1 (SF-1), OMIM 184757)
• Familial glucocorticoid deficiency (ACTH resistance) (gene MC2R/MRAP, OMIM 202200)
• Triple A (ACTH resistance, achalasia, alacrima) (gene AAAS, OMIM 231550)
• IMAGe (intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenital and genital anomalies) syndrome (X-linked, OMIM 300290)
Metabolic diseases
• Adrenoleukodystrophy (X-linked) (gene ABCD1, OMIM 300100)
• Smith-Lemli-Opitz syndrome (gene DCHR7, OMIM 270400)
• Kearns-Sayre syndrome (gene mitochondrial DNA deletions, OMIM 530000)
Disorders associated with isolated aldosterone deficiency
• Pseudohypoaldosteronism, type 1 (AR) (gene ENaC, OMIM 264350)
• Pseudohypoaldosteronism, type 1 (AD) (gene MR, OMIM 177735)
• Pseudohypoaldosteronism, type 2 (AR) (gene WNK4;WNK1, OMIM 145260)
• Corticosterone methyl oxidase deficiency I (gene CYP11B2, OMIM 124080)
• Corticosterone methyl oxidase deficiency I (gene CYP11B2, OMIM 610600)
Acquired
• Autoimmune adrenalitis, isolated
• Autoimmune polyendocrine syndrome type 1 (gene AIRE, OMIM 240300)
• Autoimmune polyendocrine syndrome type 2 (gene MICA5.1 & HLA-DR3/DQ2, OMIM 269200)
• Hemorrhage or infarction due to:
o Trauma
o Waterhouse-Friderichsen syndrome
o Anticoagulation
o Drug effects (aminoglutethimide, mitotane, ketoconazole, metyrapone, medroxyprogesterone, megestrol, etomidate, rifampin, phenytoin, barbiturates)
o Infection
o Virus (HIV, cytomegalovirus)
o Fungus (coccidiomycosis, histoplasmosis, blastomycosis, cryptococcosis)
o Mycobacterium (tuberculosis)
o Amebic
o Infiltrative
o Hemochromatosis, histiocytosis, sarcoidosis, amyloidosis
o Neoplasm
SECONDARY
Hypothalamus
Congenital
• Septo-optic dysplasia (gene HESX1, OMIM 182230)
• Corticotropin releasing hormone deficiency (gene CRH, OMIM 122560)
• Maternal hypercortisolemia
Acquired
• Inflammatory disorders
• Trauma
• Radiotherapy
• Surgery
• Tumors
• Infiltrative disease (sarcoidosis, histocytosis X)
• Steroid withdrawal after prolonged administration
Pituitary
Congenital
• Pituitary hormone deficiency, combined (gene POU1F1/PIT1, OMIM 173110, gene PROP-1, OMIM 601538)
• Proopiomelanocortin deficiency (gene POMC, OMIM 609734)
• Proconvertase 1 (gene PCSK1, OMIM 600955)
• Isolated ACTH deficiency (gene TBX19/TPIT, OMIM 604614)
Acquired
• Trauma
• Tumor (craniopharyngioma)
• Radiotherapy
• Lymphocytic hypophysitis
• Steroid withdrawal after prolonged administration

Table 1: Causes of adrenal cortical insufficiency.

triple A syndrome (ACTH resistance, alacrima, and achalasia). This clinical picture is caused by mutations in the AAAS gene encoding a protein of uncertain function [20]. In contrast, an isolated form of ACTH resistance is caused by a different genetic defect in the gene encoding the ACTH receptor, MC2R. The latter syndrome is characterized by a familial form of glucocorticoid deficiency associated with hyperpigmentation and hypoglycemia without accompanying systemic abnormalities [21]. In the category of inflammatory and immune disorders, granulomatous diseases such as sarcoid, quite rare in the <20 year old age group [22], or histiocytosis [23] can cause pituitary failure leading to secondary adrenal insufficiency.

The risk of adrenal crisis in adults with primary adrenal insufficiency is slightly higher (3.8 admissions per 100 patient-years) compared with secondary adrenal insufficiency (2.5 per 100 patient-years) [12]. Information concerning mortality in secondary adrenal insufficiency mostly comes from follow-up of individuals treated with pituitary

GH. Up to a 4-fold increase in mortality has been observed compared with the general population in children treated with pituitary GH [24-27]. This is presumably because patients with one pituitary hormone deficiency are more likely to develop other hormone deficiencies over time. Deaths were often attributed to hypoglycemia or secondary adrenal insufficiency.

Management of secondary adrenal deficiency is similar to that of primary adrenal insufficiency. It is usually not helpful to measure ACTH or cortisol levels in plasma to gauge the efficacy of treatment with corticosteroids. Rather, the patient's growth, weight gain, vital signs, as his or her own sense of well-being should guide therapy.

Relative Adrenal Insufficiency in the Intensive Care Unit

Among critically ill children and adolescents, a low incremental cortisol response to ACTH does not predict mortality [28]. There is still much controversy regarding how to best look for adrenal insufficiency in hospitalized patients, as well as whether and when to treat [29]. Glucocorticoid treatment of shock remains controversial, as most of the published trials have methodologic flaws, varied endpoints, and conflicting outcomes [30]. Thus, the decision to treat a critically ill patient with glucocorticoids must be made on a case-by-case basis until further definitive evidence is available from prospective randomized trials.

Management of Acute Adrenal Insufficiency

Hypotension and lethargy are common signs at presentation of acute adrenal insufficiency; patients and family members should be taught to recognize a change in energy level or demeanor as potential warning signs in patients with an established diagnosis. Acute adrenal insufficiency may occur during febrile illness, especially one accompanied by dehydration, vomiting, and/or diarrhea. Supplemental stress dosing is required in such circumstances, and families must be instructed as to proper management. Individuals who are unable to tolerate oral fluids and/or medications or stress doses during an illness require parenteral isotonic fluids and glucocorticoid administration. In the absence of diarrhea, a temporizing option is to administer rectal hydrocortisone suppositories [31].

Once the patient is seen in the emergency department, a large-bore intravenous catheter should be inserted for repletion of intravascular volume with saline solutions containing at least 5% dextrose due to the risk of hypoglycemia in adrenal crisis. If the patient's adrenal status is unknown, blood should be drawn for cortisol, electrolytes, glucose, ACTH, plasma renin activity, and aldosterone, preferably before exogenous steroids are administered. If acute and severe adrenal insufficiency is suspected, however, treatment should not by delay while waiting results of diagnostic testing. Simultaneous with the administration of fluids, stress doses of glucocorticoids should be given parenterally. Hydrocortisone is the treatment of choice because of its quick onset of action and mineralocorticoid activity [32].

Prednisone and dexamethasone are long-acting glucocorticoids with a slower onset of biologic action; neither has mineralocorticoid activity. Table 2 lists the relative potencies of various steroid medications. Prednisone is not an ideal choice for treating acute adrenal crisis because it must be converted to prednisolone to be effective. Dexamethasone does not cross-react in cortisol assays, so a diagnostic ACTH stimulation test may be performed right after its administration.

Liberal quantities of intravenous sodium chloride accompanied by large doses of hydrocortisone will usually restore normotension and correct electrolyte abnormalities, obviating mineralocorticoid treatment or pressor agents in adrenal crisis. As vital signs stabilize, glucocorticoids and fluid infusions are tapered over several days. Once the patient is able to eat and take oral medications, oral glucocorticoids may be substituted at regular maintenance doses, generally about 10 $mg/m^2/day$; fludrocortisone is given in primary adrenal insufficiency if aldosterone production is inadequate. Supplemental sodium chloride may be provided if dietary salt intake is low.

Chronic Replacement Therapy

Maintenance glucocorticoid replacement therapy is based on estimated normal cortisol secretion rates [33]. Glucocorticoid dosing must be individually adjusted to avoid signs and symptoms of adrenal insufficiency while also avoiding the growth retardation and Cushingoid features that can accompany overtreatment. Once growth is complete, longer-acting glucocorticoids such as prednisone or dexamethasone may be considered to enhance compliance. In general, lower doses of glucocorticoids are required to treat Addison disease compared with CAH. It is not usually helpful to measure plasma cortisol or ACTH levels in titrating the glucocorticoid dose. Patients with low serum sodium, high potassium, and/or increased plasma renin activity should receive daily oral fludrocortisone and sodium chloride supplements, adjusted to normalize these analytes. The patient's own sense of well-being, energy level, and blood pressure can help guide the adequacy of therapy in patients with Addison disease. Frequent headaches, lethargy, nausea, vomiting and/or abdominal pain may indicate inadequate treatment. Objective signs of inadequate replacement therapy are orthostatic pulse and/or blood pressure changes. If skin hyperpigmentation becomes more prominent in primary adrenal insufficiency, plasma ACTH levels may be helpful in guiding therapy. DHEA is not recommended to treat adolescent or older women with adrenal insufficiency, low energy or loss of libido [34].

As with any chronic condition, adherence to the prescribed medical regimen over time is of the essence. In this regard, improved patient education about the necessity of adherence and stress dosing, particularly at transition from adolescent to adult care, is important to avoid loss of such patients to follow-up [35,36].

Stress Dosing

Patients with adrenal insufficiency (primary or secondary, and patients with CAH) must be informed about their need to increase their glucocorticoid dose during stress to prevent a potentially lethal adrenal crisis. All such patients should wear a medical alert tag and carry an emergency medical information card, letter or diagnosis and contact information on their mobile phone to ensure that medical providers know about their underlying disorder.

Mild physical stresses such as immunizations, uncomplicated viral illnesses, and low-grade fever (temperature <38.5°C) do not require stress doses of glucocorticoids. Athletic activity and emotional stress also do not usually require a boost in glucocorticoid dose. In one study, adolescents with CAH who received an additional morning dose of hydrocortisone causing a 100% increase in serum cortisol level did not show any improvement in athletic performance [37]. More severe stresses such as illness accompanied by higher fever (temperature ^{3} 38.5°C), surgery, and major trauma should be accompanied by tripling of oral hydrocortisone maintenance doses (distributed every 8 hours) to prevent hypoglycemia, hypotension, and cardiovascular collapse.

Supplemental parenteral hydrocortisone is suggested before general

Drug	Potency Relative to Cortisol	Equivalent Cortisol Dose	Mineralocorticoid Activity
Cortisol (hydrocortisone)	1	100	+
Cortisone	0.8	125	+
Prednisone	5	20	−
Prednisolone	5	20	−
Methylprednisolone	6	17	−
Dexamethasone	50	2	−

Table 2: Glucocorticoid potencies (+ indicates present; −, absent.).

anesthesia and surgery. Doses are empiric and are not determined by evidence-based guidelines [38]. Stress doses should not be excessive, and should be tapered rapidly until the patient is able to resume his oral maintenance doses.

Adrenocortical Hyperfunction

The spectrum of disorders causing adrenal hyperfunction (Table 3) is more limited compared with those causing hypofunction.

Premature adrenarche, obesity and polycystic ovarian syndrome

The early onset of adrenal androgen secretion accompanied by pubic hair (pubarche) is termed premature adrenarche. Adrenal androgen excess is most commonly observed in children with early onset of pubic and body hair growth. The traditional age limit has been 8 years for the onset of pubic hair in girls and 9 years in boys. The lowest age limit for girls has been contested after a large cross-sectional US study revealed the relatively common occurrence of either early pubic hair or breast enlargement in healthy black girls after age 6 years and in white girls after age 7 years [39].

Laboratory evaluation of premature adrenarche

Premature adrenarche is heralded by mildly increased levels of DHEA and DHEA-sulfate. These hormone levels tend to be consistent with the child's Tanner stage of pubic hair. DHEA, a weak androgen, is the most abundantly produced adrenal steroid. The sulfated form has a longer half-life in the circulation and thus is not subject to circadian variability, making it a robust screening tool. Premature adrenarche is generally considered a benign condition that does not warrant treatment with glucocorticoid suppression. Presence of isolated pubic hair or axillary hair with or without apocrine body odor below age 8 does not necessarily presage early breast development and menstruation in girls. In most cases, children with premature adrenarche do not manifest rapid statural growth or advanced bone age. An exception is in the case of obesity or rapid weight gain, when statural growth and bone age are often inappropriate for chronologic age. With the high prevalence of obesity, bone age cannot be used as a guide for determining the need for medical treatment to suppress puberty.

Endocrine evaluation should be reserved for those children who manifest unusually early and rapidly progressive signs of puberty, including crossing centiles for statural growth, breast or testicular enlargement, or nonisosexual puberty (e.g. a girl with hirsutism or other signs of virilization, or a prepubertal boy with gynecomastia).

Obese children and adolescents secrete more adrenal sex hormones than lean children [40] and can metabolize these weak adrenal sex hormones in fat to more active sex hormones. Consequently, they may develop secondary sexual characteristics at an earlier-than-average age. In contrast to non-obese children with premature adrenarche, obese children often show advanced bone ages [41], but are not usually short.

Most overweight and obese individuals who are growing in height at a normal pace do not have a causal underlying endocrine disease. Thus, the primary care provider should not embark on an extensive evaluation in search of hormonal abnormalities without due cause. Rather, they should advise and institute dietary counseling and propose a rigorous exercise program to determine whether weight gain can be controlled before obesity becomes severe and difficult to reverse. Telephone consultation with a pediatric endocrinologist is advised if in doubt.

Obese adolescent females are hard to differentiate on clinical grounds from adrenal hyperplasia or Polycystic Ovarian Syndrome (PCOS) with respect to the cardinal signs of oligomenorrhea, hirsutism and acne. Measuring an early morning (prior to 0800) serum 17-hydroxyprogesterone by tandem mass spectrometry (LC/MS/MS) is an excellent screening test, which can largely exclude Nonclassic CAH (NCAH). However, there are no specific diagnostic tests to prove the diagnosis of PCOS, especially among adolescents. Measurement of total testosterone, sex hormone binding globulin and DHEA-sulfate are useful, as well as other endocrine tests, such as FSH, LH, estradiol, prolactin and thyroid functions in oligo- or amenorrhea. Since weight management is beneficial in both cases, lifestyle changes should be encouraged before considering medical treatment, after excluding NCAH and other pathologic causes of androgenic symptoms [42].

Cushing Syndrome

Cushing syndrome refers to any form of glucocorticoid excess, whereas Cushing disease refers to glucocorticoid excess due to ACTH hypersecretion. Although Cushing disease is rare, it is the most frequently identified non-iatrogenic etiology for glucocorticoid excess in adolescents, estimated at about 0.5 per million persons per year [43]. Table 3 lists causes of glucocorticoid excess.

History and physical examination

Prominent clinical features of adrenocortical hyper-function in adolescents are excess central body weight gain with stunted statural growth. It should be emphasized that most obese individuals do not have Cushing syndrome and do not require screening, unless growth arrest or other suspicious signs are observed. An obese adolescent with statural growth arrest should be referred to a pediatric endocrinologist for more complete evaluation. Examination of annual school photographs can often help reveal subtle changes in physiognomy and habitus over time. Other characteristic findings are easy bruisability, broad, purplish striae over the abdomen and flanks, a prominent dorsal fat pad, hyperglycemia and hypertension.

Therapeutic glucocorticoids are in widespread use for a variety of inflammatory and neoplastic diseases. Exogenous administration of relatively high doses of these drugs over long periods of time by any route is the most common cause of Cushing syndrome as well as secondary adrenal insufficiency. Although the relative safety of alternate-day oral and inhaled glucocorticoids has been demonstrated, individual differences in drug metabolism or sensitivity may cause Cushingoid effects. It is therefore important to obtain a thorough medication history in children treated with these drugs. If possible, exogenous glucocorticoids should be tapered as soon as is practical while substituting other therapeutic agents. In some patients, attenuation of Cushingoid features and improvement of statural growth may take months to years [44].

Laboratory evaluation of suspected cushing syndrome

Clinical suspicion of Cushing syndrome in the absence of exogenous glucocorticoids administration should prompt appropriate

•	**Iatrogenic**
o	Glucocorticoid or mineralocorticoid treatment
o	ACTH treatment
o	Pituitary
•	**Pituitary tumors**
•	**Adrenal tumors**
o	Carcinoma
o	Adenoma
•	**Adrenal nodular hyperplasia**
o	Carney complex (AD) (gene PRKAR1A; OMIM 160980)
o	McCune-Albright syndrome (gene GNAS1; OMIM 174800)
•	**Ectopic ACTH-producing tumors**
•	**Apparent mineralocorticoid excess (gene HSD11B2; OMIM 218030)**
•	**Glucocorticoid remediable hyperaldosteronism (AD) (genechimeric CYP11B1/B2; OMIM 103900)**

Table 3: Causes of adrenal cortical hyperfunction.

screening diagnostic studies, primarily measurement of midnight salivary cortisol, which is easier and out-performs 24-hour urine free cortisol [45]. The diagnosis may be confirmed by finding a non-suppressed morning cortisol after dexamethasone administration. The latter test has been refined by the post-dexamethasone administration of corticotrophin-releasing hormone [46]. An inappropriately brisk rise in plasma ACTH after corticotrophin-releasing hormone suggests an ACTH-producing pituitary tumor, and MRI with attention to this portion of the brain is indicated. If the tumor cannot be localized by imaging, selective catheterization of the inferior petrosal sinuses with measurement of ACTH level on both sides should be done at a specialized center. Ancillary laboratory studies frequently reveal impaired glucose tolerance and low bone density on radiographs or Dual x-ray Absorptiometry (DXA) [46].

Adrenal carcinomas (but not typically adenomas) will secrete cortisol as well as mineralocorticoids and androgens. Adrenal tumors are the most common cause of endogenous steroid excess in young children. The typical case appears in a round-faced, ruddy child with rapidly advancing premature pubarche, hypertension, and an abdominal mass. If adrenal carcinoma is suspected on the basis of ACTH-independent (ie, nonsuppressible) cortisol excess, the patient should undergo additional hormone measurements of aldosterone and plasma renin activity, as well as DHEA-sulfate and androgens.

Imaging studies

Thin-slice CT or MRI of the abdomen including the adrenal glands should be performed if preliminary hormonal test results implicate an adrenal source for excess secretion of cortisol and/or other steroid hormones. Carcinoma will often show a necrotic center and/or calcification and irregular borders, whereas benign nonfunctioning adenomas are typically more similar in density to normal adrenal tissue and homogeneous. Ectopic ACTH production by carcinomas is almost never seen in the pediatric age group.

Management of cushing syndrome

Cushing disease has traditionally been treated primarily with trans-sphenoidal pituitary tumor resection. Surgical success largely depends on the skill of the surgeon and the nature of the lesion. In one recent large series, the cure rate for peri-adolescents was 86-93% [47]. Data show that directed radiotherapy, such as gamma knife [48] and linear accelerator [49] techniques, can also induce gradual remission of ACTH hypersecretion in recurrent or refractory cases. Patients who cannot undergo surgery or newer radiotherapies may benefit from several drugs to inhibit glucocorticoid synthesis or action [50]. Once ACTH levels have decreased, the patient needs chronic glucocorticoid replacement therapy.

Adrenal Medullary Diseases

Neuroblastoma

In young children, the most common tumor encountered is a neuroblastoma. The incidence is about 1:100 000 children under age 15 per year. The average age at diagnosis in North America is 2 years [51]. Mass screening of infants has been attempted, but this practice per se has not led to improved outcomes [52].

Relevant findings

Common presenting signs include abdominal mass, fever of unknown origin, hematuria, spinal cord compression, pathologic fracture, and hypertension. Metastases to liver and bone occur in more than 50% of cases by the time of tumor detection. Biochemical markers include plasma and urinary dopamine, vanillylmandelic acid, and homovanillic acid.

Metaiodobenzylguanidine (mIBG) with iodine-123 plays an important role in the diagnosis and staging of neuroblastoma, allowing whole-body disease assessment. This modality is highly sensitive and specific for neuroblastoma, the isotope is concentrated in >90% of tumors [53]. The medical and surgical management of such tumors depends on staging risk; there is a possibility of spontaneous regression in low-grade tumors [54].

Pheochromocytoma

In the adolescent, medullary disease is most often caused by a pheochromocytoma, although this age group comprises only about 20% of all pheochromocytomas.

History and physical examination

This rare tumor may cause either episodic or chronic hypertension, usually accompanied by tachycardia, headaches, anxiety, sweating, and/or flushing. Weight loss may also be observed. The differential diagnosis in adolescents includes panic attacks, thyrotoxicosis, and renovascular disease). The use of sympathomimetic drugs, such as cocaine, amphetamines, phencyclidine, epinephrine, phenylephrine, terbutaline, or the combination of a Monoamine Oxidase (MAO) inhibitor and the ingestion of tyramine-containing foods may all lead to symptoms suggestive of pheochromocytoma.

Laboratory evaluation of suspected adrenal medullary hypertension

Other screening tests may include 24-hour ambulatory blood pressure monitoring. The chemistry profile may demonstrate hyperglycemia and/or glycosuria. Such findings should prompt referral to appropriate specialists with subsequent measurement of plasma free metanephrines [55]. Extreme hypertension should prompt immediate emergency referral and hospitalization.

Imaging studies

Confirmatory imaging may be done by metaiodobenzylguanidine (mBIG) scan [56]. This imaging test is particularly helpful in cases where either thin-slice, contrast-enhanced CT or MRI fail to show a mass, yet biochemical tests and the clinical scenario are suspicious for pheochromocytoma. Other imaging options include positron emission tomography (PET) and the use of somatostatin analogs [57].

A careful family history should be obtained for endocrine tumors (especially medullary thyroid carcinoma and hyperparathyroidism)

	Adrenal Cortical Insufficiency	Adrenal Cortical Hyperfunction	CAH	Adrenal Medullary Hyperfunction
Congenital/Neonatal	FTT, shock	Rapid weight gain; plethora	Classic CAH F genital ambiguity; FTT, shock	Hypertension; tachycardia
Childhood	Anorexia, low energy, low body weight	Rapid weight gain; poor statural growth; hypertension	Nonclassic CAH Rapid somatic growth; early pubarche/ adrenarche	Hypertension; tachycardia; headaches
Adolescent-Adult	As above, plus depression, nausea, vomiting, headache	Cushing syndrome	F: PCOS-like picture; M & F: infertility	Episodic hypertension; tachycardia; headaches; flushing; diaphoresis

Table 4: Age and mode of presentation for adrenal disorders. Key: FTT- Failure To Thrive; CAH: Congenital Adrenal Hyperplasia; PCOS: Polycystic Ovarian Syndrome; F: Female; M: Male.

because multiple endocrine neoplasia type 2 may be associated with pheochromocytoma. Transmission is autosomal dominant. Genotyping for the RET oncogene should be performed in the proband, and if positive, other family members should be tested [58]. Other syndromes prone to adrenal tumors and/or pheochromocytomas include von Hippel Lindau disease, neurofibromatosis type 1, paraganglioma and tuberous sclerosis [59]. About 30% of young patients with pheochromocytoma have one of these familial disorders, and should therefore be genotyped. Familial cases are more often bilateral [60].

Children with a family history of familial tumor syndromes should be referred to the appropriate specialists for evaluation because early detection of affected genetic status may dictate intervention before tumors develop.

Management of Adrenal Hypertension

Calcium channel–blocking drugs such as nifedipine are primarily used to control hypertension because calcium is needed for catechol secretion. In preparation for surgery, the patient should be treated for at least a week with a drug with both alpha-adrenergic blocking (eg, phenoxybenzamine) and beta-adrenergic blocking (eg, labetalol) properties. Unopposed alpha blockade would precipitate a hypotensive crisis at surgery, whereas unopposed beta blockade would exacerbate the hypertension from endogenous epinephrine, a potent vasoconstrictor. In addition, alpha-methyl-L-tyrosine (Demser) is also used to inhibit the rate-limiting step of catechol synthesis. Since 10% of pheochromocytomas are bilateral, both adrenals should be explored at surgery. If both adrenals are removed, substitution therapy will be required for primary adrenal insufficiency. Malignancy and recurrence may occur in about 10% to 15% of cases. Careful long-term follow-up of patients with regular checks of blood pressure and catechol measurements are crucial [61].

Summary and Conclusion

This review has highlighted some of the more common disorders causing either adrenal cortical or adrenal medullary dysfunction. Since these diseases are often insidious in onset and present with non-specific signs and symptoms, it is important to recognize them and consider in patients with unremitting and unexplained problems such as are described above. Table 4 summarizes the age and mode of presentation for the various categories of adrenal dysfunction. Future therapeutic challenges include developing glucocorticoid replacement drugs that more closely mimic physiologic cortisol secretion without causing Cushing syndrome. An important educational goal is to raise awareness of adrenal insufficiency in patients, families and clinicians to avoid excess morbidity and mortality.

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