

Adrenal disorders can present in variety of ways.

ADRENAL HYPERANDROGENISM

The primary adrenal androgens are dehydroepiandrosterone (DHEA) and DHEA sulfate.

The adrenal glands are a prominent source of androgen. Excess adrenal androgen secretion is a well-recognized cause of virilization in infants and children, and an occasional cause of hirsutism and virilization in women.

Prepubertal children — In prepubertal children of both sexes, androgen excess from any source increases height velocity, somatic development, and skeletal maturation. Epiphyseal fusion may occur prematurely, leading to short adult height.

Other findings vary with the sex of the child:

- In prepubertal boys, increases in androgen exposure causes virilization manifested by penile enlargement, growth of hair in androgen-dependent areas, deepening of the voice, and development of other secondary sexual characteristics (eg, isosexual precocious puberty).
- In prepubertal girls, androgen excess causes hirsutism, acne, and clitoromegaly (eg, heterosexual precocious puberty).

Pubertal children — In pubertal boys, androgen excess increases the rate of progression of puberty and skeletal maturation, which can lead to premature epiphyseal fusion, thereby decreasing adult height.

In pubertal girls, androgen excess causes virilization, primary or secondary amenorrhea, and increased skeletal maturation. As in boys, concurrent hypercortisolism may cause gonadal suppression and stunt linear growth.

Adults — In adult men, adrenal androgen excess has little effect (ie, hair growth or muscle mass do not increase; however, acne and hirsutism in early puberty may occur). It does, however, inhibit gonadotropin secretion so that testes size, testicular testosterone secretion, and spermatogenesis may decrease.

In adult women, increased adrenal androgen production causes hirsutism, acne, male pattern baldness, menstrual irregularities, oligomenorrhea or amenorrhea, infertility, and even frank virilization. As in men, hypercortisolism in women inhibits pituitary-gonadal secretion, causing oligomenorrhea or amenorrhea and infertility, but not signs of androgen excess.

The treatment and prognosis of patients with adrenal hyperandrogenism vary with the underlying cause.

Premature adrenarche — Premature adrenarche is an incomplete, benign, slowly progressive form of premature puberty that is an extreme variant of normal or nearly normal. It is a form of androgen excess, most often manifest as premature pubarche, that is characterized by a serum steroid pattern typical of adrenarche (DHEAS level above 40 $\mu\text{g}/\text{dl}$) and is otherwise unexplained. No treatment is needed besides reassurance. Pubertal development usually begins at the expected time. When associated with obesity or insulin resistance, appropriate advice for diet and lifestyle changes should be given. Children with an unusual amount of sexual hair, evidence of true pubertal development (breast development in girls, testicular enlargement in boys), or significantly advanced bone age should undergo further evaluation.

When associated with late onset congenital adrenal hyperplasia, oral contraceptives or glucocorticoid replacement is given.

Classic 21-hydroxylase deficiency results in one of two clinical syndromes: a salt-losing form and the simple virilizing form. Girls with both forms present as neonates with ambiguous genitalia. Boys present as neonates with a salt-losing adrenal crisis (salt-losing form) (hyponatremia, hyperkalemia, and failure to thrive) or as toddlers with signs of puberty (simple virilizing form).

- Reproductive abnormalities are common in females and include structural abnormalities due to androgen excess in utero and anovulatory menstrual cycles.
- In adult men, testicular masses (adrenal rests), Leydig cell dysfunction, and abnormal semen analyses may be seen.
- Nonclassic or late-onset 21-hydroxylase deficiency may present as hirsutism and menstrual irregularity in young women, early pubarche or sexual precocity in school age children, or there may be no symptoms.

Glucocorticoid replacement is necessary in all infants and children who have classic 21-hydroxylase deficiency. In infants and children, this is usually administered as hydrocortisone in a dose of 10 to 15 mg/m^2 body surface area/day. Mineralocorticoid replacement is necessary in all pediatric patients who have classic 21-hydroxylase deficiency.

Common causes are autoimmune disease, metastasis, infection, drugs or congenital adrenal hyperplasia. Adrenoleukodystrophy and adrenomyeloneuropathy, an X-linked disorder, should be considered in any boy or young man with adrenal insufficiency. Congenital adrenal hypoplasia should be suspected in neonates with salt wasting and hyperpigmentation. Boys with X-linked forms may also have a failure of puberty (DAX-1). 46,XY individuals with sex reversal or ambiguous genitalia may have steroidogenic factor 1 (SF-1) mutations.

Familial glucocorticoid deficiency presents in infancy with low cortisol and high corticotropin (ACTH) but normal mineralocorticoid production. IMAGE (intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, genital abnormalities) and Triple A syndrome (adrenal insufficiency, achalasia, alacrima and neurologic abnormalities) should be suspected in the context of their additional syndromic features.

The most common clinical features of chronic primary adrenal insufficiency are chronic malaise, lassitude, fatigue, weakness, anorexia, and weight loss.

Other clinical manifestations are gastrointestinal symptoms, nausea, vomiting, pain abdomen, diarrhea, salt craving, joint pains, hypotension, electrolyte abnormalities (hyponatremia and hyperkalemia), hypoglycemia and hyperpigmentation.

Adrenal crisis is a life-threatening emergency that requires immediate treatment with steroids like hydrocortisone. Fludrocortisone is given as mineralocorticoid replacement.

ADRENAL TUMORS

Unilateral tumors or masses of the adrenal gland are common. They are categorized as either functional (hormone-secreting) or silent, and as either benign or malignant.

- The majority of adrenocortical tumors are benign, nonfunctioning adenomas that are discovered incidentally on abdominal imaging studies (adrenal incidentalomas).
- Others are benign hormone-secreting adenomas that cause Cushing's syndrome, primary aldosteronism or, much less commonly, virilization or feminization. Pheochromocytomas are adrenomedullary, not adrenocortical tumors.
- Adrenocortical carcinomas (ACCs) are rare, frequently aggressive tumors that may be functional and cause Cushing's syndrome and/or virilization, or nonfunctional, and present as an abdominal mass or an incidental finding.
- At initial presentation, approximately 50 percent of adult patients with ACC have relatively advanced disease stage.

Adults with hormone-secreting ACCs usually present with Cushing's syndrome alone (45 percent), or a mixed Cushing's and virilization syndrome, with overproduction

of both glucocorticoids and androgens (25 percent). Fewer than 10 percent present with virilization alone, but the presence of virilization in a patient with an adrenal neoplasm suggests an ACC rather than an adenoma.

The clinical symptoms associated with glucocorticoid excess, such as weight gain, weakness, and insomnia, usually develop very rapidly (over three to six months). Patients who have coexisting hypersecretion of adrenal androgens may not experience the typical catabolic effects of glucocorticoid excess (muscle and skin atrophy). Feminization and hyperaldosteronism occur in fewer than 10 percent of cases.

Most patients with nonfunctioning tumors (or more precisely with subclinical production of steroids) present with clinical manifestations related to tumor growth (ie, abdominal or flank pain), or with an incidentally found adrenal mass detected on radiographic imaging performed for a different reason; constitutional symptoms. Uncommonly, a varicocele or fever and leucocytosis from tumor necrosis or production of chemokines may occur.

Children usually present with virilization (84 percent) while isolated glucocorticoid excess (Cushing's syndrome) is much less common (6 percent).

Congenital Adrenal tumors — Surgery is the treatment of choice for all patients with hormone-secreting adrenal tumors. Surgery is the initial treatment for patients with adrenocortical carcinoma.

Androgen and estrogen-secreting tumors — Androgen-secreting adrenal tumors are usually malignant, but benign tumors have also been described in women. In a report of 21 women with androgen-secreting tumors, malignant tumors (n = 10) were larger at presentation than benign tumors (n = 11; 14 versus 9 cm, respectively). In addition, serum testosterone levels were 2.6-fold higher in the women with malignant tumors. Benign cortisol-secreting adenomas can also produce small amounts of androgens, but the serum androgen levels are usually not elevated.

Estrogen-secreting tumors are rare and are usually malignant. In males it can present as feminization with gynecomastia, decreased libido, testicular atrophy; in women it can present with breast tenderness and dysfunctional uterine bleeding.

For patients with potentially resectable stage I to III adrenocortical cancer who are surgical candidates, complete open surgical resection is recommended as initial therapy. Suspicious lymph nodes should be resected, but the benefit of routine lymphadenectomy has not been fully established yet. Adjuvant mitotane therapy is recommended for all patients who have a high risk of disease recurrence after complete resection, including all those with high-grade disease (Ki67 >10 percent or mitotic rate greater than 20 per 50 high-power fields [HPF]), incompletely resected disease, intraoperative tumor spillage or fracture, and some large tumors that are low grade but have vascular or capsular invasion.

CUSHING SYNDROME

Various causes of adrenal cushing syndrome are Adrenocortical adenomas and carcinomas – 18 to 20 percent.

- Primary pigmented nodular adrenocortical disease (PPNAD), also called bilateral adrenal micronodular hyperplasia – less than 1 percent
- Bilateral macronodular adrenal hyperplasia (BMAH) – less than 1 percent

The most common manifestations of Cushing's syndrome, such as obesity, hypertension, and glucose intolerance, are less suggestive of the presence of hypercortisolism as they are also common in individuals who do not have adrenal hyperfunction.

Symptoms that are most suggestive of the presence of hypercortisolism include supraclavicular fat pads, skin atrophy, wide purplish striae, and proximal muscle weakness.

Adenomas are always cured with unilateral adrenalectomy. Laparoscopic adrenalectomy is the preferred approach for adrenal adenomas. There may be cardiovascular and metabolic benefits to surgery for patients with subclinical Cushing's syndrome, who often present with adrenal incidentalomas.

ACTH-independent bilateral adrenal hyperplasia – There are two forms of ACTH-independent bilateral adrenal hyperplasia: primary pigmented nodular adrenocortical disease (PPNAD, also called micronodular adrenal hyperplasia); and bilateral macronodular adrenal hyperplasia (BMAH).

- Surgical bilateral adrenalectomy is uniformly effective in PPNAD; subtotal or unilateral adrenalectomy should not be performed since recurrence can occur. Bilateral adrenalectomy is also indicated in most patients with macronodular adrenal hyperplasia. In selected cases with macronodular adrenal hyperplasia and aberrant hormone receptors, pharmacologic blockade on the aberrant receptor can result in long-term normalization of cortisol secretion.
- Although medical treatment does not cure ACTH-independent micronodular or macronodular adrenal hyperplasia, the adrenal enzyme inhibitors metyrapone or ketoconazole can be given to reduce cortisol secretion in an attempt to improve the patient's physical condition before surgery. As with adrenocortical tumors, ACTH secretion will not increase and override the pharmacologic blockade.

ADRENAL INCIDENTALOMA

An adrenal incidentaloma is a mass lesion greater than 1 cm in diameter, serendipitously discovered by radiologic examination. This entity is the result of technological advances in imaging such as computed tomography (CT) and magnetic resonance imaging (MRI).

All patients with adrenal incidentalomas should

be evaluated for the possibility of malignancy and subclinical hormonal hyperfunction. A homogeneous adrenal mass < 4 cm in diameter, with a smooth border, and an attenuation value < 10 Hounsfield unit (HU) on unenhanced CT, and rapid contrast medium washout (eg, >50 percent at 10 minutes) is very likely to be a benign cortical adenoma. The imaging characteristics that suggest adrenal carcinoma or metastases include: irregular shape, inhomogeneous density, high unenhanced CT attenuation values (>20 HU), delayed contrast medium washout (eg, <50 percent at 10 minutes), diameter >4 cm, and tumor calcification.

Pheochromocytoma should be excluded in all patients by measuring 24-hour urinary fractionated metanephrines and catecholamines. Symptoms (self-limited episodes of nonexertional palpitations, diaphoresis, headache, tremor, or pallor) are present in approximately 50 percent of patients with pheochromocytoma, and when present, they are typically paroxysmal. If the adrenal mass is vascular, or there are other features suggestive of pheochromocytoma, the preferred test is plasma fractionated metanephrines. Surgery is recommended for all patients with biochemical documentation of pheochromocytoma after preoperative alpha adrenergic blockade.

Subclinical Cushing's syndrome should be ruled out by performing the 1 mg overnight dexamethasone suppression test (DST). To detect significant glucocorticoid secretory autonomy, the post-overnight DST 8 AM serum cortisol concentration cutoff is >1.8 mcg/dL (>138 nmol/L). An abnormal 1 mg overnight dexamethasone suppression is consistent with adrenocorticotrophic hormone (ACTH)-independent cortisol production, a finding that should be confirmed with 24-hour urinary free cortisol or 2 day low dose DST.

Surgical resection of adenoma is also recommended for patients with subclinical Cushing's syndrome who are younger and who have disorders potentially attributable to excess glucocorticoid secretion (eg, recent onset of hypertension, diabetes, obesity, and low bone mass) If the adrenal incidentaloma patient is hypertensive, a plasma aldosterone-to-plasma renin activity ratio and plasma potassium concentration should be obtained to screen for primary aldosteronism. Primary aldosteronism may be associated with resistant hypertension, which is defined as failure to achieve goal blood pressure despite adherence to an appropriate three-drug regimen including a diuretic. Although hypokalemia is considered to be a "classic" sign of primary aldosteronism, some patients with primary aldosteronism due to an adrenal adenoma, and more commonly those with adrenal hyperplasia, are not hypokalemic.

For most patients with confirmed unilateral aldosterone hypersecretion (eg, adrenal adenoma or unilateral adrenal hyperplasia), unilateral adrenalectomy is recommended over medical therapy. For patients with bilateral adrenal hyperplasia be treated with medical therapy, not adrenalectomy. For patients with either bilateral adrenal

306 hyperplasia or confirmed unilateral adrenal aldosterone hypersecretion (who refuse or are not candidates for surgery), mineralocorticoid receptor antagonist like spironolactone or eplerenone is recommended.

Surgical resection is recommended for patients with adrenal masses greater than 4 cm in diameter. However, the clinical scenario, imaging characteristics, and patient age frequently guide the management decisions in patients who have adrenal incidentalomas that fall on either side of the 4 cm diameter cutoff.

In a patient with a known primary malignancy elsewhere who has a newly discovered adrenal mass that has an imaging phenotype consistent with metastatic disease, performing a diagnostic CT-guided fine-needle aspiration (FNA) biopsy may be indicated, but only after excluding pheochromocytoma with biochemical testing. Adrenal biopsy would not be needed if the patient was already known to have widespread metastatic disease. Excision of a tumor is recommended if the initial imaging phenotype is suspicious.

For all adrenal masses larger than 10 cm, including those masses with benign imaging phenotypes, open adrenalectomy rather than a laparoscopic procedure is recommended.

For incidentalomas with a benign appearance on imaging, repeat imaging study at 6 to 12 months after initial discovery is recommended. Whether to obtain additional images (eg, at 6, 12, and 24 months after initial discovery) and the type of image obtained (eg, CT, MRI, or ultrasound) should be guided by clinical judgment and imaging phenotype. Removal of any tumor that enlarges by more than 1 cm in diameter during the follow-up period is recommended.

We suggest that overnight DST be repeated annually for four years in cases where initial evaluation is negative, although the yield and cost-effectiveness of such testing is also unknown. Autonomous function (glucocorticoid) not present at baseline may be detected at follow-up testing.

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