DISEASES OF ENDOCRINE SYSTEM. CHRONIC INSUFFICIENCY OF ADRENAL CORTEX GLANDS. ETIOLOGY, PATHOGENESIS, CLINICAL PRESENTATION, DIAGNOSIS, PREVENTION AND TREATMENT. ACUTE INSUFFICIENCY OF ADRENAL CORTEX GLANDS. HORMONAL-ACTIVE TUMORS OF ADRENAL GLANDS

*Methodological recommendations
for students of IV course*

ЗАХВОРЮВАННЯ ЕНДОКРИННОЇ СИСТЕМИ. ХРОНІЧНА НЕДОСТАТНІСТЬ КОРИ НАДНИРКОВИХ ЗАЛОЗ. ЕТІОЛОГІЯ, ПАТОГЕНЕЗ, КЛІНІКА, ДІАГНОСТИКА, ПРОФІЛАКТИКА ТА ЛІКУВАННЯ. ГОСТРА НЕДОСТАТНІСТЬ КОРИ НАДНИРКОВИХ ЗАЛОЗ. ГОРМОНАЛЬНО-АКТИВНІ ПУХЛИНИ НАДНИРКОВИХ ЗАЛОЗ

Методичні вказівки для студентів IV курсу

**Харків
ХНМУ
2013**

Compilers   L.V. Zhuravlyova,
              V.O. Fedorov
              M.V. Filonenko
              O.O. Yankevich
              O.M. Krivonosova
              M.O. Oliynyk

Упорядники   Л.В. Журавльова
              В.О. Федоров
              М.В. Філоненко
              О.О. Янкевич
              О.М. Кривоносова
              М.О. Олійник

MODULE № 1 "**THE FUNDAMENTALS OF DIAGNOSIS, TREATMENT AND PREVENTION OF MAIN DISEASES OF THE ENDOCRINE SYSTEM**"

TOPIC "CHRONIC INSUFFICIENCY OF ADRENAL CORTEX GLANDS. ETIOLOGY, PATHOGENESIS, CLINICAL PRESENTATION, DIAGNOSIS, PREVENTION AND TREATMENT. ACUTE INSUFFICIENCY OF ADRENAL CORTEX GLANDS. HORMONAL-ACTIVE TUMORS OF ADRENAL GLANDS"

The purpose:
1. To acquaint students with the functional anatomy and physiology of adrenal glands.
2. To acquaint students with etiology, pathogenesis, clinical presentation, diagnosis, prevention and treatment of Chronic Insufficiency of Adrenal Cortex glands (Addison's disease) and Acute Adrenal Insufficiency.
3. To acquaint students with classification of Tumors of Adrenal Glands.
4. To acquaint students with clinical presentation, diagnosis, treatment of Cushing's syndrome.
5. To acquaint students with clinical presentation, diagnosis, treatment of Conn's syndrome.
6. To acquaint students with etiology, pathogenesis, clinical features, diagnosis and treatment of Pheochromocytoma.
7. To acquaint students with clinical forms, diagnosis and treatment of Congenital Adrenal Hyperplasia.

What a student should know?
1. Adrenal anatomy and function.
2. Determination, epidemiology, etiology, pathogenesis, clinical presentation, diagnosis, prevention and treatment of Chronic Insufficiency of Adrenal Cortex glands (Addison's disease) and Acute Adrenal Insufficiency.
3. Classification of Tumors of Adrenal Glands.
4. Clinical presentation, diagnosis, treatment of Cushing's syndrome.
5. Clinical presentation, diagnosis, treatment of Cushing's syndrome.
6. Clinical presentation, diagnosis, treatment of Conn's syndrome.
7. Etiology, pathogenesis, clinical features, diagnosis and treatment of Pheochromocytoma.
8. Determination, clinical forms, diagnosis and treatment of Congenital Adrenal Hyperplasia.

What a student should be able to do?
1. To recognize clinical symptoms.
2. To analyze the results of hormonal assays and functional tests.
3. To perform differential diagnostics.
4. To draft the plan of examination and treatment.

5. To diagnose Chronic Insufficiency of Adrenal Cortex glands (Addison's disease), Tumors of Adrenal Glands.
6. To treat patients with Chronic Insufficiency of Adrenal Cortex glands (Addison's disease), Tumors of Adrenal Glands.
7. To draft long term plan in patients with Chronic Insufficiency of Adrenal Cortex glands (Addison's disease), Tumors of Adrenal Glands.
8. To diagnose Acute Adrenal Insufficiency and Addison's disease in condition of stress.

Content of topic:
"Chronic insufficiency of adrenal cortex glands. Etiology, pathogenesis, clinical presentation, diagnosis, prevention and treatment. Acute insufficiency of adrenal cortex glands. Hormonal-active tumors of adrenal glands"

The normal adrenal glands weigh 6–11 g each. They are located above the kidneys and have their own blood supply. Arterial blood flows initially to the subcapsular region and then meanders from the outer cortical zona glomerulosa through the intermediate zona fasciculata to the inner zona reticularis and eventually to the adrenal medulla. The right suprarenal vein drains directly into the vena cava while the left suprarenal vein drains into the left renal vein. During early embryonic development, the adrenals originate from the urogenital ridge and then separate from gonads and kidneys about the 6th week of gestation. Concordant with the time of sexual differentiation (seventh to ninth week of gestation), the adrenal cortex starts to produce cortisol and the adrenal sex steroid precursor DHEA. The orphan nuclear receptors SF1 (steroidogenic factor 1) and DAX1 (dosage-sensitive sex reversal gene 1), among others, play a crucial role during this period of development, as they regulate a multitude of adrenal genes involved in steroidogenesis.

Histologically, the cortex is divided into three zones, but these function as two units (zona glomerulosa and zonae fasciculata/reticularis) which produce corticosteroids in response to humoral stimuli. The adrenal cortex produces several hormones. The most important are aldosterone (a mineralocorticoid), cortisol (a glucocorticoid), and androgen and estrogen (sex hormones). These hormones manage metabolism and body characteristics, such as hair growth and body shape. The adrenal cortex secretes 3 types of hormones: (1) mineralocorticoids (the most important of which is aldosterone), which are secreted by the zona glomerulosa; (2) glucocorticoids (predominantly cortisol), which are secreted by the zona fasciculata and, to a lesser extent, the zona reticularis; and (3) adrenal androgen (mainly dehydroepiandrosterone [DHEA]), which is predominantly secreted by the zona reticularis, with small quantities released from the zona fasciculata. All adrenocortical hormones are steroid compounds derived from cholesterol. Cortisol binds to proteins in the blood, mainly cortisol-binding globulin or transcortin. More than 90% of cortisol is transported in the blood in this bound form. In contrast, only 50% of aldosterone is bound to protein in the

4

blood. All adrenocortical steroids are degraded in the liver and predominantly conjugated to glucuronides, with lesser amounts of sulfates formed. About 75% of these degradation products are excreted in the urine, and the rest is excreted in the stool by means of the bile.

Mineralocorticoids

Aldosterone accounts for 90% of mineralocorticoid activity, with some activity contributed by deoxycorticosterone, corticosterone, and cortisol. The normal concentration of aldosterone in the blood ranges from 2–16 ng/dL supine and 5–41 ng/dL upright, although the concentration exhibits diurnal variation, and the secretory rate is generally 150–250 mcg/d.

Aldosterone promotes sodium reabsorption and potassium excretion by the renal tubular epithelial cells of the collecting and distal tubules. As sodium is reabsorbed, water follows passively, leading to an increase in the extracellular fluid volume with little change in the plasma sodium concentration. Persistently elevated extracellular fluid volumes cause hypertension. This helps minimize further increases in extracellular fluid volume by causing a pressure diuresis in the kidney, a phenomenon known as aldosterone escape. Without aldosterone, the kidney loses excessive amounts of sodium and, consequently, water, leading to severe dehydration.

As sodium is actively reabsorbed, potassium is excreted. Imbalances in aldosterone thus lead to hypokalemia and muscle weakness if levels are increased and to hyperkalemia with cardiac toxicity if levels are decreased. In addition to sodium being exchanged for potassium at the renal tubules, hydrogen is also exchanged, although to a much lesser extent. Therefore, with aldosterone excess, mild metabolic alkalosis may develop. In addition to the effects of aldosterone on the renal tubules, a smaller but similar effect is noted on the sweat glands and salivary glands. Aldosterone stimulates sodium chloride reabsorption and potassium secretion in the excretory ducts, which helps prevent excessive salivation and conserve body salt in hot climates. Aldosterone also affects sodium absorption in the intestine, especially the colon. Deficiency may cause a watery diarrhea from the unabsorbed sodium and water. Many factors affect aldosterone secretion, the most important of which involve the renin-angiotensin system and changes in the plasma potassium concentration.

Activation of the renin-angiotensin system: The juxtaglomerular apparatus senses decreased blood flow to the kidney secondary to hypovolemia, hypotension, or renal artery stenosis and releases renin in response. Renin is an enzyme that activates angiotensinogen to release angiotensin I. In the lung, ACE converts angiotensin I to angiotensin II, a potent vasoconstrictor and stimulator of aldosterone release by the adrenal gland.

Concentration of potassium in the extracellular fluid: Increases in the plasma potassium concentration stimulate the release of aldosterone to encourage potassium excretion by the kidney.

Concentration of sodium in the extracellular fluid: Decreases in sodium concentration also stimulate aldosterone release.

Adrenocorticotropic hormone (ACTH) secretion: ACTH secreted by the anterior pituitary primarily affects release of glucocorticoids by the adrenal but, to a lesser extent, also stimulates aldosterone release.

Glucocorticoids

Approximately 95% of glucocorticoid activity comes from cortisol, with corticosterone, a glucocorticoid less potent than cortisol, making up the rest. The normal cortisol concentration in the blood averages 12 mcg/dL, with a secretory rate averaging 15–20 mg/d. Cortisol release is almost entirely controlled by the secretion of ACTH by the anterior pituitary gland, which is controlled by corticotropin-releasing hormone (CRH) secreted by the hypothalamus. In normal situations, CRH, ACTH, and cortisol secretory rates demonstrate a circadian rhythm, with a zenith in the early morning and a nadir in the evening. Various stresses also stimulate increased ACTH and, thus, cortisol secretion. A negative feedback effect of cortisol on the anterior pituitary and the hypothalamus help control these increases and regulate plasma cortisol concentrations.

Cortisol has many effects on the body.

- Cortisol stimulates gluconeogenesis in the liver by stimulating the involved enzymes and mobilizing necessary substrates, specifically amino acids from muscle and free fatty acids from adipose tissue. It simultaneously decreases glucose use by extrahepatic cells in the body. The overall result is an increase in serum glucose (ie, adrenal diabetes) and increased glycogen stores in the liver.
- Cortisol decreases protein stores in the body, except in the liver, by inhibiting protein synthesis and stimulating catabolism of muscle protein.
- Cortisol has clinically significant anti-inflammatory effects, blocking the early stages of inflammation by stabilizing lysosomal membranes, preventing excessive release of proteolytic enzymes, decreasing capillary permeability and, consequently, edema, and decreasing chemotaxis of leukocytes. In addition, it induces rapid resolution of inflammation that is already in progress.
- Immunity is adversely affected. Eosinophil and lymphocyte counts in the blood decrease with atrophy of lymphoid tissue.

Adrenal androgens

The adrenal cortex continually secretes several male sex hormones, including DHEA, DHEA sulfate (DHEAS), androstenedione, and 11-hydroxyandrostenedione, with small quantities of the female sex hormones progesterone and estrogen. Most of the effects result from extra-adrenal conversion of the androgens to testosterone. All have weak effects, but they likely play a role in early development of the male sex organs in

childhood, and they have an important role in women during pubarche. ACTH has a definite stimulatory effect on androgen release by the adrenal. Therefore, secretion of these hormones parallels that of cortisol.

Adrenal Medulla. The adrenal medulla is a completely different entity. Epinephrine (80%) and norepinephrine (20%), with minimal amounts of dopamine, are secreted into the bloodstream due to direct stimulation by acetylcholine release from sympathetic nerves. Preganglionic sympathetic nerve fibers pass from the intermediolateral horn cells of the spinal cord through the sympathetic chains and splanchnic nerves, without synapsing, into the adrenal medulla. These hormones are responsible for an increase in cardiac output and vascular resistance and for all the physiologic characteristics of the stress response.

Addison's Disease (Chronic Insufficiency of Adrenal Cortex glands)

Adrenal insufficiency results from inadequate secretion of cortisol and/or aldosterone.

Thomas Addison first described the clinical presentation of primary adrenocortical insufficiency (Addison disease) in 1855 in his classic paper, On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules.

Epidemiology

The prevalence of well-documented, permanent adrenal insufficiency is 5 in 10,000 in the general population. Hypothalamicpituitary origin of disease is most frequent, with a prevalence of 3 in 10,000, whereas primary adrenal insufficiency has a prevalence of 2 in 10,000. Approximately one-half of the latter cases are acquired, mostly caused by autoimmune destruction of the adrenal glands; the other one-half are genetic, most commonly caused by distinct enzymatic blocks in adrenal steroidogenesis affecting glucocorticoid synthesis (i.e. congenital adrenal hyperplasia.)

Etiology

Primary adrenal insufficiency is most commonly caused by autoimmune adrenalitis. Isolated autoimmune adrenalitis accounts for 30–40%, whereas 60–70% develop adrenal insufficiency as part of autoimmune polyglandular syndromes (APS). APS1, also termed APECED (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy), is the underlying cause in 10% of patients affected by APS. APS1 is transmitted in an autosomal recessive manner and is caused by mutations in the autoimmune regulator gene AIRE. Associated autoimmune conditions overlap with those seen in APS2, but may also include total alopecia, primary hypoparathyroidism, and, in rare cases, lymphoma. APS1 patients invariably develop chronic mucocutaneous candidiasis, usually manifest in childhood, and preceding adrenal insufficiency by years or decades. The much more prevalent APS2 is of polygenic inheritance, with confirmed associations with the HLA-DR3 gene region in the major histocompatibility complex and distinct gene regions involved in immune regulation (CTLA-4,

PTPN22, CLEC16A). Coincident autoimmune disease most frequently includes thyroid autoimmune disease, vitiligo, and premature ovarian failure. Less commonly, additional features may include type 1 diabetes and pernicious anemia caused by vitamin B_{12} deficiency. X-linked adrenoleukodystrophy has an incidence of 1:20,000 males and is caused by mutations in the X-ALD gene encoding the peroxisomal membrane transporter protein ABCD1; its disruption results in accumulation of very long chain (>24 carbon atoms) fatty acids. Approximately 50% of cases manifest in early childhood with rapidly progressive white matter disease (cerebral ALD); 35% present during adolescence or in early adulthood with neurologic features indicative of myelin and peripheral nervous system involvement (adrenomyeloneuropathy, AMN). In the remaining 15%, adrenal insufficiency is the sole manifestation of disease. Of note, distinct mutations manifest with variable penetrance within affected families. Rarer causes of adrenal insufficiency involve destruction of the adrenal glands as a consequence of infection, hemorrhage, or infiltration (Table 342-7); tuberculous adrenalitis is still a frequent cause of disease in developing countries. Adrenal metastases rarely cause adrenal insufficiency, and this occurs only with bilateral, bulky metastases. Inborn causes of primary adrenal insufficiency other than congenital adrenal hyperplasia are rare, causing less than 1% of cases.

However, their elucidation provides important insights into adrenal gland development and physiology. Mutations causing primary adrenal insufficiency include factors regulating adrenal development and steroidogenesis (DAX-1, SF-1), cholesterol synthesis, import and cleavage (DHCR7, StAR, CYP11A1), and elements of the adrenal ACTH response pathway (MC2R, MRAP).

Secondary adrenal insufficiency is the consequence of dysfunction of the hypothalamic-pituitary component of the HPA axis. Excluding iatrogenic suppression, the overwhelming majority of cases are caused by pituitary or hypothalamic tumors, or their treatment by surgery or irradiation. Rarer causes include pituitary apoplexy, either as a consequence of an infarcted pituitary adenoma or transient reduction in the blood supply of the pituitary during surgery or after rapid blood loss associated with parturition, also termed Sheehan's syndrome. Isolated ACTH deficiency is rarely caused by autoimmune disease or pituitary infiltration. Mutations in the ACTH precursor POMC or in factors regulating pituitary development are genetic causes of ACTH deficiency.

Clinical manifestations

Patients usually present with features of both glucocorticoid and mineralocorticoid deficiency. The predominant symptoms vary depending on the duration of disease.

Patients may present with clinical features of chronic Addison disease or in acute addisonian crisis precipitated by stress factors such as infection, trauma, surgery, vomiting, diarrhea, or noncompliance with replacement steroids.

8

The onset of symptoms most often is insidious and nonspecific.

Hyperpigmentation of the skin and mucous membranes often precedes all other symptoms by months to years. It is caused by the stimulant effect of excess adrenocorticotrophic hormone (ACTH) on the melanocytes to produce melanin.

Hyperpigmentation usually is generalized but most often prominent on the sun-exposed areas of the skin, extensor surfaces, knuckles, elbows, knees, and scars formed after the onset of disease. Scars formed before the onset of disease (before the ACTH is elevated) usually are not affected. Palmar creases, nail beds, mucous membranes of the oral cavity (especially the dentogingival margins and buccal areas), and the vaginal and perianal mucosa may be similarly affected.

Hyperpigmentation, however, need not be present in every long-standing case and may not be present in cases of short duration.

Other skin findings include vitiligo, which most often is seen in association with hyperpigmentation in idiopathic autoimmune Addison disease. It is due to the autoimmune destruction of melanocytes.

Almost all patients complain of progressive weakness, fatigue, poor appetite, and weight loss. Prominent gastrointestinal symptoms may include nausea, vomiting, and occasional diarrhea. Glucocorticoid-responsive steatorrhea has been reported. Dizziness with orthostasis due to hypotension occasionally may lead to syncope. This is due to the combined effects of volume depletion, loss of the mineralocorticoid effect of aldosterone, and loss of the permissive effect of cortisol in enhancing the vasopressor effect of the catecholamines. Myalgias and flaccid muscle paralysis may occur due to hyperkalemia. Patients may have a history of using medications known to affect adrenocortical function or to increase cortisol metabolism. Other reported symptoms include muscle and joint pains; a heightened sense of smell, taste, and hearing; and salt craving. Patients with diabetes that previously was well-controlled may suddenly develop a marked decrease in insulin requirements and hypoglycemic episodes due to an increase in insulin sensitivity. Impotence and decreased libido may occur in male patients, especially in those with compromised or borderline testicular function. Female patients may have a history of amenorrhea due to the combined effect of weight loss and chronic ill health or secondary to premature autoimmune ovarian failure. Steroid-responsive hyperprolactinemia may contribute to the impairment of gonadal function and to the amenorrhea.

Physical examination in long-standing cases most often reveals increased pigmentation of the skin and mucous membranes, with or without areas of vitiligo. Patients show evidence of dehydration, hypotension, and orthostasis. Female patients may show an absence of axillary and pubic hair and decreased body hair. This is due to loss of the adrenal androgens, a major source of androgens in women. Addison disease caused by another specific disease may be accompanied by clinical features of that disease. Calcification of the ear and costochondral junctions is described but is a rare physical finding.

Diagnosis

In patients presenting with chronic illness, investigations should be performed before any treatment. In patients with suspected acute adrenal crisis, treatment should not be delayed pending results. A random blood sample should be stored for measurement of cortisol. It may be appropriate to spend 30 minutes performing a short ACTH stimulation test before administering hydrocortisone, but investigations may need to be delayed until after recovery. Assessment of glucocorticoids Random plasma cortisol is usually low in patients with adrenal insufficiency, but it may be within the normal range, yet inappropriately low for a seriously ill patient. Random measurement of plasma cortisol cannot therefore be used to confirm or refute the diagnosis, unless the value is high (>460 nmol/L (>17 mg/dL)). More useful is the short ACTH stimulation test (also called the tetracosactrin or short Synacthen test) described in Box 20.46. Cortisol levels fail to increase in response to exogenous ACTH in patients with primary or secondary adrenal insufficiency. These can be distinguished by measurement of ACTH (which is low in ACTH deficiency and high in Addison's disease). If an ACTH assay is unavailable, then a long ACTH stimulation test can be used (1 mg depot ACTH i.m. daily for 3 days); in secondary adrenal insufficiency there is a progressive increase in plasma cortisol with repeated ACTH administration, whereas in Addison's disease, cortisol remains less than 700 nmol/L (25.4 μg/dL) at 8 hours after the last injection. In a patient who is already receiving glucocorticoids, the short ACTH stimulation test can be performed first thing in the morning, more than 12 hours after the last dose of glucocorticoid, or the treatment can be changed to a synthetic steroid such as dexamethasone (0.75 mg daily), which does not cross-react in the plasma cortisol immunoassay.

Assessment of mineralocorticoids

Mineralocorticoid secretion in patients with suspected Addison's disease cannot be adequately assessed by electrolyte measurements since hyponatraemia occurs in both aldosterone and cortisol deficiency. Hyperkalaemia is common, but not universal, in aldosterone deficiency. Plasma renin activity and aldosterone should be measured in the supine position. In mineralocorticoid deficiency, plasma renin activity is high, with plasma aldosterone being either low or in the lower part of the normal range.

Assessment of adrenal androgens

This is not necessary in men because testosterone from the testes is the principal androgen. In women, dehydroepiandrosterone (DHEA) and androstenedione may be measured in a random specimen of blood, though levels are highest in the morning.

Other tests to establish the cause

Patients with unexplained secondary adrenocortical insufficiency should be investigated. In patients with elevated ACTH, further tests are required to establish the cause of Addison's disease. In those who have autoimmune adrenal

10

failure, antibodies can often be measured against steroid-secreting cells (adrenal and gonad), thyroid antigens, pancreatic β cells and gastric parietal cells. Thyroid function tests, full blood count (to screen for pernicious anaemia), plasma calcium, glucose and tests of gonadal function should be performed. Other causes of adrenocortical disease are usually obvious clinically, particularly if health is not fully restored by corticosteroid replacement therapy. Tuberculosis causes adrenal calcification, visible on plain X-ray or ultrasound scan. A chest X-ray and early morning urine for culture should also be taken. An HIV test should be performed if risk factors for infection are present. Imaging of the adrenals by CT or MRI to identify metastatic malignancy may also be appropriate.

Treatment

Glucocorticoid replacement for the treatment of chronic adrenal insufficiency should be administered at a dose that replaces the physiologic daily cortisol production, which is usually achieved by the oral administration of 15–25 mg hydrocortisone in two to three divided doses. Pregnancy may require an increase in hydrocortisone dose by 50% during the last trimester. In all patients, at least one-half of the daily dose should be administered in the morning. Currently available glucocorticoid preparations fail to mimic the physiologic cortisol secretion rhythm. Long-acting glucocorticoids such as prednisolone or dexamethasone are not preferred as they result in increased glucocorticoid exposure due to extended glucocorticoid receptor activation at times of physiologically low cortisol secretion. There are no well-established dose equivalencies, but as a guide, equipotency can be assumed for 1 mg hydrocortisone, 1.6 mg cortisone acetate, 0.2 mg prednisolone, 0.25 mg prednisone, and 0.025 mg dexamethasone. Monitoring of glucocorticoid replacement is mainly based on the history and examination for signs and symptoms s uggestive of glucocorticoid over- or under-replacement, including assessment of body weight and blood pressure. Plasma ACTH, 24-hour urinary free cortisol, or serum cortisol day curves reflectwhether hydrocortisone has been taken or not, but do not convey reliable information about replacement quality. In patients with isolated primary adrenal insufficiency, monitoring should include screening for autoimmune thyroid disease, and female patients should be made aware of the possibility of premature ovarian failure. Supraphysiologic glucocorticoid treatment with doses equivalent to 30 mg hydrocortisone or more will affect bone metabolism, and these patients should undergo regular bone mineral density evaluation. All patients with adrenal insufficiency need to be instructed about the requirement for stressrelated glucocorticoid dose adjustments. These generally consist of doubling the routine oral glucocorticoid dose in the case of intercurrent illness with fever and bedrest and the need for IV hydrocortisone injection at a daily dose of 100 mg in cases of prolonged vomiting, surgery, or trauma. Patients living or traveling in regions with delayed access to acute health care should carry a hydrocortisone self-injection emergency kit, in addition to their usual steroid emergency cards and bracelets.

Mineralocorticoid replacement in primary adrenal insufficiency hould be initiated at a dose of 100–150 μg fludrocortisone. The adequacy of treatment can be evaluated by measuring blood pressure, sitting and standing, to detect a postural drop indicative of hypovolemia. In addition, serum sodium, potassium, and plasma renin should be measured regularly. Renin levels should be kept in the upper normal reference range. Changes in glucocorticoid dose may also impact on mineralocorticoid replacement as cortisol also binds the mineralocorticoid receptor; 40 mg hydrocortisone is equivalent to 100 μg fludrocortisone. In patients living or traveling in areas with hot or tropical weather conditions, the fludrocortisone dose should be increased by 50–100 μg during the summer. Mineralocorticoid dose may also need to be adjusted during pregnancy, due to the antimineralocorticoid activity of progesterone, but this is less often required than hydrocortisone dose adjustment. Plasma renin cannot serve as a monitoring tool during pregnancy, as renin rises physiologically during gestation.

Patients should avoid any stress conditions (infections, physical or mental overworking).

ACUTE ADRENAL INSUFFICIENCY

Acute adrenal insufficiency usually occurs after a prolonged period of nonspecific complaints and is more frequently observed in patients with primary adrenal insufficiency, due to the loss of both glucocorticoid and mineralocorticoid secretion. Postural hypotension may progress to hypovolemic shock. Adrenal insufficiency may mimic features of acute abdomen with abdominal tenderness, nausea, vomiting, and fever. In some cases, the primary presentation may resemble neurologic disease, with decreased responsiveness, progressing to stupor and coma. An adrenal crisis can be triggered by an intercurrent illness, surgical or other stress, or increased glucocorticoid inactivation (e.g., hyperthyroidism).

1. The Waterhouse-Friderichsen Syndrome

The bacterial infection leads to massive hemorrhage into one or (usually) both adrenal glands. It is characterized by overwhelming bacterial infection meningococcemia leading to massive blood invasion, organ failure, coma, low blood pressure and shock, disseminated intravascular coagulation with widespread purpura, rapidly developing adrenocortical insufficiency and death. Multiple species of bacteria can be associated with the condition: Meningococcus is another term for the bacterial species Neisseria meningitidis; blood infection with said species usually underlies WFS. While many infectious agents can infect the adrenals, an acute, selective infection is usually Meningococcus. Pseudomonas aeruginosa can also cause WFS. WFS can also be caused by Streptococcus pneumoniae infections, a common bacterial pathogen typically associated with meningitis in the adult and elderly population. Mycobacterium tuberculosis could also cause WFS. Tubercular invasion of the adrenal glands could cause hemorrhagic destruction of the glands and cause mineralocorticoid

deficiency. Staphylococcus aureus has recently also been implicated in pediatric WFS. It can also be associated with Haemophilus influenzae. Cytomegalovirus can cause adrenal insufficiency, especially in the immunocompromised. Signs and symptoms. WFS is the most severe form of meningococcal septicemia. The onset of the illness is nonspecific with fever, rigors, vomiting, and headache. Soon a rash appears; first macular, not much different from the rose spots of typhoid, and rapidly becoming petechial and purpuric with a dusky gray color. Low blood pressure (hypotension) is the rule and rapidly leads to septic shock. The cyanosis of extremities can be impressive and the patient is very prostrated or comatose. In this form of meningococcal disease, meningitis generally does not occur. There is hypoglycemia with hyponatremia and hyperkalemia, and the ACTH stimulation test demonstrates the acute adrenal failure. Leukocytosis need not to be extreme and in fact leukopenia may be seen and it is a very poor prognostic sign. C-reactive protein levels can be elevated or almost normal. Thrombocytopenia is sometimes extreme, with alteration in prothrombin time (PT) and partial thromboplastin time (PTT) suggestive of diffuse intravascular coagulation (DIC). Acidosis and acute renal failure can be seen as in any severe sepsis. Meningococci can be readily cultured from blood or CSF, and can sometimes be seen in smears of cutaneous lesions. Dysphagia, atrophy of the tongue, and cracks at the corners of the mouth are also characteristic features.

2. Addisonian crisis

In an emergency, anyone with Addison's disease can experience symptoms of extreme weakness, a serious drop in blood pressure and mental confusion. This means they need extra steroid medication immediately, and may need an emergency injection. As a general rule, an Addisonian should give themselves an emergency injection of 100 mg hydrocortisone sodium (Efcortesol or Solu-Cortef) if they vomit more than once. The causes of an Addisonian crisis: severe physical shock, e.g. a car accident; severe infection, e.g. flu with a high temperature; severe dehydration, e.g. stomach bug with vomiting The symptoms of an Addisonian crisis: extreme weakness, mental confusion, extreme drowsiness, in advanced cases slipping towards a coma, pronounced dizziness, nausea and/or vomiting, severe headache, abnormal heart rate – either too fast or too slow, abnormally low blood pressure, feeling extremely cold, possibly a fever, possibly abdominal tenderness.

3. Unilateral adrenalectomy in Cushing's syndrome or glucocorticosteroma

4. Congenital Adrenal aplasia

5. Metastasis to Adrenal glands

6. Dysfunction of adrenal cortex in stress conditions

7. Withdrawal symptoms in patients with long-term corticosteroid therapy

8. Diseases of the hypothalamic-pituitary with deficiency of adreno-corticotropic hormone

9. CNS disease: brain tumor, meningitis, encephalitis, optic nerve glioma

10. Adrenogenital syndrome

Acute adrenal insufficiency (AAI) is a rare but severe condition caused by a sudden defective production of adrenal steroids (cortisol and aldosterone). It represents an emergency, thus the rapid recognition and prompt therapy are critical for survival even before the diagnosis is made. The disease may occur at any age. The onset is often sudden. The initial presentation may be limited to abdominal pain, nausea, vomiting and fever. Hypoglycemic seizures or symptoms of dehydration are common manifestations seen in children. If untreated, shock and bilateral adrenal hemorrhage can rapidly lead to death.

The clinical signs are nonspecific but the diagnosis of AAI is suspected if a patient presents with hypotonia or shock that responds poorly to catecholamines. Laboratory exams show signs of adrenal insufficiency (hypoglycemia, hyponatremia and elevated natriuresis, hyperkaliemia, hemoconcentration, hypochloremic metabolic acidosis and functional renal failure) confirmed by hypocortisolemia, increased ACTH, and an insufficient response to rapid ACTH stimulation testing that leads to the diagnosis of absolute and peripheral AAI. The mineralocorticoid insufficiency, when present, can be confirmed by low aldosterone levels and high plasma renin activity (PRA). The etiological diagnosis is based on various imaging exams (CT-scan, ultrasound, or MRI). In case of anterior pituitary insufficiency, ACTH is low. Secondary adrenal insufficiency needs to be eliminated. Peritonitis is often a differential diagnosis as well as other causes of adrenal destruction such as bilateral adrenalectomy, Waterhouse-Friderichsen syndrome, autoimmune adrenalitis, infectious adrenalitis and tumour infiltration.

Acute adrenal insufficiency requires immediate initiation of rehydration, usually carried out by saline infusion at initial rates of 1 L/h with continuous cardiac monitoring. Glucocorticoid replacement should be initiated by bolus injection of 100 mg hydrocortisone, followed by the administration of 100–200 mg hydrocortisone over 24 h, either by continuous infusion or provided by several IV or IM injections. Mineralocorticoid replacement can be initiated once the daily hydrocortisone dose has been reduced to <50 mg because at higher doses hydrocortisone provides sufficient stimulation of mineralocorticoid receptors. Prognosis varies depending on the etiologies, but is generally correlated with the rapidity of diagnosis and medical assistance. Death is rare when the patients receive appropriate medical assistance.

PRIMARY ALDOSTERONISM (CONN'S SYNDROME)

Although initially considered a rarity, primary aldosteronism now is considered one of the more common causes of secondary hypertension (HTN). Litynski reported the first cases, but Conn was the first to well characterize the disorder, in 1956. Conn syndrome, as originally described, refers specifically to primary aldosteronism due to the presence of an adrenal aldosteronoma (aldosterone-secreting benign adrenal neoplasm).

Based on older data, it was originally estimated that primary aldosteronism accounted for less than 1% of all patients with HTN. Subsequent data, however, indicated that it may actually occur in as many as 5-15% of patients with HTN. Primary aldosteronism may occur in an even greater percentage of patients with treatment-resistant HTN and may be considerably underdiagnosed; this is especially true if patients with treatment-refractory HTN are not specifically referred for evaluation to an endocrinologist.)

Although primary aldosteronism is still a considerable diagnostic challenge, recognizing the condition is critical because primary aldosteronism–associated HTN can often be cured (or at least optimally controlled) with the proper surgical or medical intervention. The diagnosis is generally 3-tiered, involving an initial screening, a confirmation of the diagnosis, and a determination of the specific subtype of primary aldosteronism.

Although prior studies suggested that aldosteronomas were the most common cause of primary aldosteronism (70–80% of cases), later epidemiologic work indicated that the prevalence of aldosteronism due to bilateral idiopathic adrenal hyperplasia (IAH; sometimes also abbreviated as BAH) is higher than had previously been believed. These reports suggested that IAH may be responsible for as many as 75% of primary aldosteronism cases. Moreover, reports have described a rare syndrome of primary aldosteronism characterized by histologic features intermediate between adrenal adenoma and adrenal hyperplasia, which often is unilaterally localized (also referred to earlier literature as "intermediate aldosteronism").

Physical Examination

The clinical presentation of primary aldosteronism is not distinctive, and the correct diagnosis requires a high index of suspicion on the part of the physician. The common clinical scenarios in which the possibility of primary aldosteronism should be considered include the following:

- Patients with spontaneous or unprovoked hypokalemia, especially if the patient is also hypertensive
- Patients who develop severe and/or persistent hypokalemia in the setting of low to moderate doses of potassium-wasting diuretics
- Patients with treatment-refractory/-resistant hypertension (HTN)

Patients with severe hypokalemia report fatigue, muscle weakness, cramping, headaches, and palpitations. They can also have polydipsia and polyuria from hypokalemia-induced nephrogenic diabetes insipidus. Long-standing HTN may lead to cardiac, retinal, renal, and neurologic problems, with all the associated symptoms and signs.

Familial primary aldosteronism

The 2 major familial varieties of primary aldosteronism are glucocorticoid-remediable aldosteronism (GRA; type 1 familial primary aldosteronism) and a

non–glucocorticoid-remediable type (type 2 familial primary aldosteronism). The recognition of GRA is particularly important because of its implications for patients who are hypertensive and whose family members are apparently unaffected. HTN, strokes, and other significant cardiovascular events are described in young persons with this syndrome. Although the syndrome is uncommon, heightened levels of suspicion are essential for the diagnosis. Fewer than 200 well-validated cases exist in the literature. All patients with GRA should be treated medically with glucocorticoids and without surgery. Although uncommon, GRA may be more prevalent than was previously presumed. A significant subgroup of patients with the milder normokalemic variety of this syndrome is probably incorrectly presumed to have essential HTN. A family history of HTN (particularly with a young age of onset), HTN in children, low-renin HTN, and presumed IAH are the typical situations in which this diagnosis should be considered. The third type of familial PA, due to mutations in the KCNJ5 potassium channel-coding gene, is considered to be exceedingly rare, but can also lead to HTN and hypokalemia at a very early age.

Patients with primary aldosteronism do not present with distinctive clinical findings, and a high index of suspicion based on the patient's history is vital in making the diagnosis. The findings could include the following:

- Hypertension (HTN) – This condition almost invariably occurs, although a few rare cases of primary aldosteronism unassociated with HTN have been described in the literature.
- Weakness
- Abdominal distention
- Ileus from hypokalemia
- Findings related to complications of HTN – These include cardiac failure, hemiparesis due to stroke, carotid bruits, abdominal bruits, proteinuria, renal insufficiency, hypertensive encephalopathy (confusion, headache, seizures, changes in the level of consciousness), and hypertensive retinal changes.

It is important to note that primary aldosteronism in and of itself is typically not associated with edema, despite the volume-expanded state associated with it. The lack of edema results from spontaneous natriuresis and diuresis (called the "aldosterone escape") that occurs in patients with primary aldosteronism and that appears to be mediated by atrial natriuretic peptide (ANP). Of note, this effect is probably based on the activation of the apical ATP/UTP/P2Y2 receptor system (at the connecting tubule/collecting duct level), leading to increased presentation of sodium, which, in turn, induces closure of the epithelial sodium channel (ENaC), with resultant decrease in sodium reabsorption (ie, enhanced natriuresis). Hence, the finding of significant edema in patients who are presumed to have aldosteronism suggests either that a wrong diagnosis has been made or that associated complications, such as renal or cardiac failure, are present.

16

Tests

Therapeutic trial of spironolactone (*Aldactone*) (this procedure is also no longer used as a diagnostic test for primary aldosteronism, because easier and more rapid alternatives exist; hence, it is currently of historic value. For reasons of completeness, the spironolactone therapeutic trial involved the administration of spironolactone orally at a dose of 100 mg 4 times daily for 5 weeks. A positive test would be characterized by a decrease in diastolic blood pressure of at least 20 mm Hg).

Screening (First-Tier) Tests

Serum potassium and bicarbonate levels

Hypokalemia and metabolic alkalosis have low sensitivities and specificities for primary aldosteronism when these levels are tested by themselves. Hypokalemia (serum potassium level <3.6 mEq/L) has a sensitivity of 75–80% while the patient is on a normal sodium diet. Typically, it is associated with mild metabolic alkalosis (serum bicarbonate level >31 mEq/L) and inappropriate kaliuresis (urinary potassium excretion >30 mmol/day).

Sodium and magnesium levels

Mild serum hypernatremia in the 143–147 mEq/L range and mild hypomagnesemia from renal magnesium wasting are other associated biochemical findings in established primary aldosteronism.

Plasma aldosterone/plasma renin activity ratio

Because the random plasma aldosterone/plasma renin activity (PRA) ratio is fairly constant over many physiologic conditions, it can be used for screening. Normal values are less than 270 when aldosterone concentration is expressed in pmol/L, or are less than 10 when aldosterone concentration is expressed in ng/dL.

Algorithm for screening for potential primary aldosteronism.

When aldosterone is measured in ng/dL and PRA is measured in ng/mL/h, a plasma aldosterone/PRA ratio of greater than 20–25 has 95% sensitivity and 75% specificity for primary aldosteronism. When aldosterone is measured in pmol/L, a ratio greater than 900 is consistent with primary aldosteronism.

Medication interference

The plasma aldosterone/PRA ratio should not be calculated when the patient is taking medications that can interfere with this measurement. Spironolactone, an aldosterone receptor antagonist, should be stopped for 6 weeks prior to testing. Eplerenone, another aldosterone receptor antagonist, can also interfere with testing and should be stopped for at least 2 weeks before testing.

Alpha-blockers, such as doxazosin, do not interfere with the PA/PRA ratio. Beta-blockers and calcium channel blockers do not affect the diagnostic accuracy of the ratio in most cases.

PRA after salt and water depletion and/or upright posture

In primary aldosteronism, PRA is less than 1 ng/mL/h and fails to rise above 2 ng/mL/h following salt and water depletion, furosemide administration,

or 4 hours of erect posture. This test, along with the captopril suppression tests, has been used either as a screening test or as a confirmatory (second-tier) test for primary aldosteronism, depending on personal preferences of various groups involved in primary aldosteronism research.

Confirmatory tests are based on the concept that aldosterone is secreted in an unregulated fashion in primary aldosteronism and therefore cannot be suppressed by usual physiologic regulatory inputs. In a similar fashion, the PRA is chronically and tonically suppressed and cannot be stimulated

Captopril and losartan suppression tests

This involves the oral administration of a single dose of captopril (25–50 mg), an ACE inhibitor. In healthy individuals, aldosterone levels will be suppressed to less than 15 ng/dL. The test has a sensitivity of 90–100% but a specificity of only 50–80%.

Serum aldosterone level

After 3 days of an unrestricted sodium diet and 1 hour of full recumbency, healthy individuals have aldosterone levels of less than 15 ng/dL. When serum aldosterone is elevated above 22 ng/dL and renin is suppressed, the serum aldosterone (S-Aldo) test virtually confirms the diagnosis of primary aldosteronism. However, because aldosterone secretion is variable, the negative and positive predictive value of a single random aldosterone level is limited.

As many as 40% of patients with primary aldosteronism have serum aldosterone levels that remain within the reference range on repeated testing, as is typically the case in essential hypertension (HTN).

Algorithm for confirmation of primary aldosteronism.

24-Hour urinary aldosterone excretion test

The 24-hour urinary aldosterone (U-Aldo) excretion test is one of the most useful confirmatory diagnostic tools because it is an index for total daily aldosterone secretion (in a fashion similar to the 24-h urinary free cortisol [UFC], which is typically elevated in patients with Cushing syndrome).

In most patients with primary aldosteronism, the 24-hour U-Aldo is greater than 14 mcg/day (after 3 days of salt loading). Only about 7% of patients with primary aldosteronism have values of less than 14 mcg/day.

Salt-loading test

The salt-loading test can be done by using either an intravenous salt-loading protocol or an oral salt-loading protocol. The oral protocol calls for daily ingestion of at least 10–12 g of sodium chloride for at least 5 days before the test is performed. When the oral protocol has been met, 24-hour U-Aldo, sodium, potassium, and creatinine excretions are measured, and serum aldosterone and PRA should be determined. In normal individuals, the major U-Aldo metabolite, urinary aldosterone-18-glucuronide, should fall below a level of 17 mcg/day. Nonsuppressibility of U-Aldo-18G is highly suggestive of primary aldosteronism. Nonetheless, this test is cumbersome and rarely performed.

Postural stimulation test

Aldosteronomas are associated with an anomalous decrease in the aldosterone level with upright posture, in contrast to patients with idiopathic adrenal hyperplasia (IAH), in whom a renin-angiotensin system (RAS)–mediated increase in aldosterone level occurs with upright posture.

Similarly, a serum aldosterone level surge occurs in patients with renin-responsive adenomas (RRAs), low-renin essential HTN, and very rare cases of unilateral adrenal hyperplasia (the latter presenting with features intermediate between idiopathic adrenal hyperplasia [IAH] and aldosterone-producing adrenal adenoma; occasionally designated as "intermediate aldosteronism").

When abdominal computed tomography (CT) and magnetic resonance imaging (MRI) scans are combined with postural stimulation, the positive predictive value (PPV) of an abnormal postural test in predicting surgically correctable primary aldosteronism due to a single adenoma is 98%.

The standard postural test protocol involves obtaining baseline values for serum aldosterone (S-Aldo) and plasma renin activity (PRA) levels, as well as these levels 2 hours after the patient has assumed an erect posture. S-Aldo levels typically rise in this setting at least 50% above baseline in healthy persons, in persons with essential HTN, and in the subgroup of patients with primary aldosteronism who have either idiopathic adrenal hyperplasia (IAH) or RRAs.

Among patients with aldosteronomas (aldosterone-producing adenomas; APAs), S-Aldo levels typically do not rise or paradoxically fall to this level. The sensitivity and specificity of this test in the differential diagnosis of the main causes of primary aldosteronism have been reported to be as high as 80–85%.

Furosemide (Lasix) stimulation test

This test is often combined with the upright posture test. The typical test involves the oral administration of 40 mg of furosemide the night before as well as the morning of the test. On the morning of the test, after the furosemide dose has been administered, the patient remains upright 2-3 hours; then, S-Aldo and PRA levels are assayed. The interpretation of the test results is similar to that described above for the postural stimulation test.

Diurnal rhythm of aldosterone

The circadian rhythm of aldosterone secretion in healthy individuals parallels that of cortisol and is corticotropin-dependent. The lowest values are observed around 11:30 pm to midnight, and the highest values occur early in the morning around 7:30–8:00 am (assuming a normal sleep-wake cycle). While this is preserved in patients with aldosteronomas, it is typically lost in patients with IAH.

CT scanning

The initial radiologic investigation in the workup of primary aldosteronism is high-resolution, thin-sliced (2–2.5 mm) adrenal CT scanning with contrast. Aldosteronomas tend to be small, in contrast to cortisol-producing adrenocortical adenomas; only aldosteronomas that are at least 1 cm in diameter can be detected reliably and consistently.

The overall sensitivity of high-resolution, thin-slice adrenal CT scanning is greater than 90%, but the picture is complicated by the many false-positive findings associated with incidentalomas, which are reported in some series to be found in up to 10–15% of the general population (their prevalence increases with age).

Moreover, high-resolution CT studies can actually be detrimental, because these scans often detect the hyperplasia accompanying adenomas and may result in a tendency to overdiagnose idiopathic adrenal hyperplasia (IAH). Similarly, because long-term adrenal hyperplasia is associated with pseudonodule and nodule formation, this radiographic picture may often be confused with the diagnosis of autonomous adenomas.

Surgical indications

Some investigators suggest that when a solitary, unilateral macroadenoma (>1 cm) is detected on a CT scan in a young patient in the setting of unequivocal aldosteronism, unilateral adrenalectomy is indicated. However, because of the age-dependent risk that a solitary, unilateral adrenal macroadenoma may be a nonfunctioning adenoma, some experts believe that adrenal vein sampling should be performed in patients older than 40 years.

MRI

It is generally accepted that MRI is not superior to contrast-enhanced CT scanning for adrenal visualization. High-resolution CT scans may actually have better adrenal definition.

Magnetic resonance imaging (MRI) scan in a patient with Conn syndrome showing a left adrenal adenoma.

Plasma and urine 18-oxocortisol (18-oxo-F)/18-hydroxycortisol may be of diagnostic use.

Fludrocortisone Suppression Test

This test works on the same principle that the sodium chloride intravenous infusion or the oral salt-loading tests are based on for confirming a diagnosis of primary aldosteronism. The fludrocortisone suppression test has lost much of its popularity, however, because it requires hospitalization of the patient and 4-5 days to complete, and it currently is mainly of historical interest.

For reasons of completeness, the description of this test is as follows: fludrocortisone is administered orally at a dose of 0.1–0.2 mg every 6 hours, along with supplemental sodium chloride and potassium. In the healthy individual, following this stimulation, the serum aldosterone (S-Aldo) level is typically suppressed to less than 8 ng/dL, with a corresponding urinary aldosterone (U-Aldo) excretion of less than 12 mcg/day.

In patients with primary aldosteronism, neither the urinary aldosterone level nor the plasma aldosterone level suppresses to the above-noted thresholds.

Dexamethasone Suppression Test

This test is relevant only in the setting of possible familial aldosteronism. Customarily, in patients with primary aldosteronism, dexamethasone is associated with a transient slight-to-moderate reduction of plasma and urinary aldosterone

levels, although not into the normal reference range. In the subset of primary aldosteronism patients with glucocorticoid-remediable aldosteronism (GRA), small doses of dexamethasone (1–2 mg/day) induce full normalization in plasma and urinary aldosterone levels. This is invariably associated with improvement in hypertension (HTN) in these patients. Other reports suggest a cut-off level for plasma aldosterone of less than 4 ng/dL and/or a relative plasma aldosterone suppression of greater than 80% of the baseline for the diagnosis of GRA following the dexamethasone challenge.

Three variants of familial primary aldosteronism exist. Type 1 familial primary aldosteronism (also called GRA) is associated with improvement in HTN using low-dose dexamethasone. Types 2 and 3 familial primary aldosteronism are not dexamethasone suppressible.

Differential diagnosis

Consider the diagnosis of primary aldosteronism in all persons with hypertension (HTN) and hypokalemia. Making the correct diagnosis may be the only way to achieve adequate blood pressure control and thus, to prevent the sequelae of poorly controlled HTN.

Conditions to consider in the differential diagnosis of primary aldosteronism include the following:

- HTN
- Malignant HTN
- Hypertensive encephalopathy
- Hypokalemia
- Metabolic alkalosis
- Renal artery stenosis
- Renovascular HTN
- Low-renin essential HTN – Constitutes about 40% of essential HTN
- Tobacco chewing
- Carbenoxolone intoxication
- Apparent mineralocorticoid excess (AME) syndrome
- Various causes of secondary aldosteronism – Unlike primary aldosteronism, these causes are associated with elevated renin (plasma renin activity) levels
- Chrétien syndrome – This rare syndrome is characterized by mineralocorticoid excess and adrenocortical HTN secondary to a pituitary adenoma producing pro-opiomelanocortin (POMC)
- Deoxycorticosterone (DOC)–secreting adrenal tumors
- Renovascular ischemia
- Preeclampsia (toxemia of pregnancy)
- Renin-secreting tumor – These are rare tumors arising from the juxtaglomerular apparatus

Additional select genetic/familial disorders and syndromes to consider include the following:

- Gitelman syndrome – This is due to a defective sodium/chloride cotransporter (NCCT); it is basically a salt-losing tubulopathy with secondary aldosteronism
- Barrter syndrome – This is a phenocopy of at least 3 distinct genetic defects (ie, hyperactivition of the sodium-potassium-dichloride cotransporter [NKCC2], the renal outer medullary potassium channel [ROMK1], or the renal epithelial chloride channel [ClCKb], the latter encoded by the barttin gene; this is also a salt-losing tubulopathy with secondary aldosteronism and is pathophysiologically similar to Gitelman syndrome
- Gordon syndrome – This is due to inactivating mutations of the serine-threonine kinases WNK1 and WNK4 ("with no lysine [K]" kinases), leading to hypertension, hyperkalemia, mild hyperchloremia, acidosis, and suppressed plasma renin activity
- Pseudoaldosteronism (Liddle syndrome) – This is a rare autosomal dominant disorder due to hyperactivating mutations of the renal epithelial sodium channel (ENaC), with excessive sodium reabsorption in the renal distal tubule; levels of renin and aldosterone are low
- 11beta-hydroxysteroid dehydrogenase deficiency
- Glucocorticoid resistance – This is due to inactivating mutations of the glucocorticoid receptor

Treatment:

Among the major goals of therapy for primary aldosteronism are (1) normalization of blood pressure, (2) normalization of levels of serum potassium and other electrolytes, and (3) normalization of serum aldosterone levels.

Diet

A low-salt diet, although helpful in achieving blood pressure control in primary aldosteronism, may be associated with false-negative results on biochemical testing. A high-salt diet makes the achievement of blood pressure control more difficult and may cause false-positive results on biochemical testing.

Pharmacologic Therapy

Calcium channel blockers

By inhibiting the intracellular calcium flux in the adrenocortical cells, the dihydropyridine calcium channel blockers reduce the production of aldosterone in response to a variety of stimulants, including potassium, corticotropin, and angiotensin-II. Nifedipine is the most extensively studied of these medications; however, although nifedipine causes a significant improvement in patients with hypertension (HTN), it does not address the pathophysiology of the condition. The plasma renin activity (PRA), aldosterone levels, plasma volume, and serum potassium concentrations remain essentially unchanged while using nifedipine.

Mineralocorticoid antagonists

Mineralocorticoid antagonists, such as spironolactone, are inhibitory ligands to the mineralocorticoid receptor (MR). They achieve remarkable blood pressure control and normalization of plasma volume and serum potassium concentrations, particularly in patients with aldosteronomas.

Glucocorticoids

In the subgroup of patients with glucocorticoid-remediable aldosteronism (GRA), the treatment of choice is the administration of the lowest possible dose of glucocorticoid that can be used to achieve adequate blood pressure control. Because of the potential adverse effects that can result from even subtle glucocorticoid excess, using short-acting glucocorticoids, such as prednisone and hydrocortisone (rather than dexamethasone), is generally best.

Other

ACE inhibitors and angiotensin receptor blockers (ARBs) are also potential treatment options. Less ideal medical treatment options include potassium-sparing diuretics, such as triamterene and amiloride, that are not mineralocorticoid antagonists. Amiloride acts at the level of the distal convoluted tubule but does not bind to mineralocorticoid receptors.

A few reports of the use of percutaneous injection of ethanol or acetic acid into aldosteronomas as a treatment modality exist; in these cases, the treatment was usually administered to patients for whom surgery was contraindicated. This technique is neither popular nor well validated. Furthermore, it requires the technical expertise of a highly skilled interventional radiologist.

Considerations

Nonsurgical therapy is also a viable treatment option in patients who have lateralizable disease but who are poor surgical candidates because of other coexisting comorbidities. It is also a viable treatment option in the rare setting of bilateral functional adrenal adenomas that would otherwise require bilateral adrenalectomy.

Adrenal Surgery

Surgery is the treatment of choice for the lateralizable variants of primary aldosteronism, including typical aldosteronomas, renin-responsive adenomas (RRAs), and primary adrenal hyperplasia (PAH).

PHEOCHROMOCYTOMA

A pheochromocytoma is a rare, catecholamine-secreting tumor that may precipitate life-threatening hypertension. The tumor is malignant in 10% of cases but may be cured completely by surgical removal. Although pheochromocytoma has classically been associated with 3 syndromes – von Hippel-Lindau (VHL) syndrome, multiple endocrine neoplasia type 2 (MEN 2), and neurofibromatosis type 1 (NF1) – there are now 10 genes that have been identified as sites of mutations leading to pheochromocytoma.

Diagnosis

Symptoms and signs of pheochromocytoma include the following:

- Headache
- Diaphoresis
- Palpitations
- Tremor
- Nausea
- Weakness
- Pallor
- Anxiety, sense of doom
- Epigastric pain
- Flank pain
- Constipation
- Weight loss

The classic history of a patient with a pheochromocytoma includes spells characterized by headaches, palpitations, and diaphoresis in association with severe hypertension. These 4 characteristics together are strongly suggestive of a pheochromocytoma. In the absence of these 3 symptoms and hypertension, the diagnosis may be excluded. The spells may vary in occurrence from monthly to several times per day, and the duration may vary from seconds to hours. Typically, they worsen with time, occurring more frequently and becoming more severe as the tumor grows.

Clinical signs associated with pheochromocytomas include the following:

- Hypertension: Paroxysmal in 50% of cases
- Postural hypotension (from volume contraction)
- Hypertensive retinopathy
- Weight loss
- Pallor
- Fever
- Tremor
- Tachyarrhythmias
- Pulmonary edema
- Cardiomyopathy
- Diabetes mellitus
- Ileus

Sinus tachycardia (presenting as palpitations) is the most common cardiac rhythm abnormality in patients with pheochromocytoma, but more serious ventricular arrhythmias or conduction disturbances may also occur. Other cardiac manifestations include reversible dilated or hypertrophic cardiomyopathy; Takotsubo cardiomyopathy has gained increasing recognition. When pheochromo-

cytoma occurs as part of a hereditary syndrome, other manifestations of the syndrome may be noted. In patients with neurofibromatosis, these include neurofibromas and café au lait spots. The latter are patches of cutaneous pigmentation that vary from 1–10 mm and can occur any place on the body; characteristic locations include the axillae and intertriginous areas (groin). The name café au lait refers to the color of the lesions, which varies from light to dark brown.

Catecholamines produced by pheochromocytomas are metabolized within chromaffin cells. Norepinephrine is metabolized to normetanephrine and epinephrine is metabolized to metanephrine. Because this process occurs within the tumor, independently of catecholamine release, pheochromocytomas are best diagnosed by measurement of these metabolites rather than by measurement of the parent catecholamines. Guidelines from the North American NeuroEndocrine Tumor Society (NANETS) recommend biochemical testing for pheochromo-cytoma in the following cases:

- Symptomatic patients
- Patients with an adrenal incidentaloma
- Patients who have a hereditary risk for developing a pheochromocytoma or paraganglioma (extra-adrenal pheochromocytoma)

The choice of diagnostic test should be based on the clinical suspicion of a pheochromocytoma. Plasma metanephrine testing has the highest sensitivity (96%) for detecting a pheochromocytoma, but it has a lower specificity (85%). General laboratory features of pheochromocytoma include the following:

- Hyperglycemia
- Hypercalcemia
- Erythrocytosis

Imaging studies should be performed only after biochemical studies have confirmed the diagnosis of pheochromocytoma. Computed tomography (CT) scanning or magnetic resonance imaging (MRI) can be used for detection of the disorder. Scintigraphy may be used when these techniques fail to localize the tumor.

Catecholamine Testing

A fractionated plasma free metanephrine level may be measured in a standard venipuncture sample, drawn about 15–20 minutes after intravenous catheter insertion. Positioning of the patient for the venipuncture is controversial. Although some experts advocate having the patient seated, NANETS guidelines recommend drawing the sample with the patient in a supine position, as tests in seated patients have a higher false-positive rate. Perform a 24-hour urine collection for creatinine, total catecholamines, vanillylmandelic acid, and metanephrines. Measure creatinine in all collections of urine to ensure adequacy of the collection. The collection container should be dark and acidified and should be kept cold to avoid degradation of the catecholamines. Optimally, collect urine during or immediately after a crisis. Some authors have reported good experience with evaluating epinephrine and norepinephrine

separately (in part to confirm the total catecholamine level and in part to determine whether levels reflect the high norepinephrine-to-epinephrine ratio expected). Separate measurement of metanephrine and normetanephrine, to confirm the total metanephrine level and the normetanephrine-to-metanephrine ratio, has also proved useful. Although dopamine is a major catecholamine, measurement of dopamine levels in 24-hour urine is not useful, because most urinary dopamine is derived from renal extraction.

CT Scanning

Abdominal CT scanning has an accuracy of 85-95% for detecting adrenal masses with a spatial resolution of 1 cm or greater but is less accurate for lesions smaller than 1 cm.

MRI

MRI is preferred for detection of pheochromocytoma in children and in pregnant or lactating women. MRI has a reported sensitivity of up to 100% in detecting adrenal pheochromocytomas, does not require contrast, and does not expose the patient to ionizing radiation. MRI is also superior to CT scanning for detecting extra-adrenal pheochromocytomas. In approximately 70% of cases, pheochromocytomas appear hyperintense on T2-weighted images (as demonstrated in the image below), because of their high water content. Axial, T2-weighted magnetic resonance imaging (MRI) scan showing large left suprarenal mass of high signal intensity on a T2-weighted image. The mass is a pheochromocytoma. Initial studies have suggested that MR spectroscopy can be used to distinguish pheochromocytomas from other adrenal masses. Specifically, a resonance signature of 6.8 ppm appears to be unique to pheochromocytomas; the signature apparently is attributable to the catecholamines and catecholamine metabolites present in pheochromocytomas.

Scintigraphy

A scan with iodine-123 (^{123}I) – labeled metaiodobenzylguanidine (MIBG) is reserved for cases in which a pheochromocytoma is confirmed biochemically but CT scanning or MRI does not show a tumor. MIBG scanning is frequently used in cases of familial pheochromocytoma syndromes, recurrent pheochromocytoma, or malignant pheochromocytoma.

Treatment

Surgical resection of the tumor is the treatment of choice for pheochromocytoma and usually results in cure of the hypertension. Careful preoperative management is required to control blood pressure, correct fluid volume, and prevent intraoperative hypertensive crises. Although there is no consensus regarding the preferred drugs for preoperative blood pressure control, alpha blockers, beta blockers, calcium channel blockers, and angiotensin receptor blockers have all been used. Start alpha blockade with phenoxybenzamine 10–14 days preoperatively to allow for expansion of blood volume. The patient should undergo volume expansion with isotonic sodium chloride solution. Encourage liberal salt intake.

26

Initiate a beta blocker only after adequate alpha blockade (usually, 2 days). If beta blockade is started prematurely, unopposed alpha stimulation could precipitate a hypertensive crisis. Administer the last doses of oral alpha and beta blockers on the morning of surgery.

Laparoscopic Adrenalectomy

Surgical mortality rates are less than 2–3% when the operation is performed by a surgeon and an anesthesiologist who are experienced. Use an arterial line, cardiac monitor, and Swan-Ganz catheter. Administer stress-dose steroids if bilateral resection is planned. An anterior midline abdominal approach was used in the past; in current practice, however, laparoscopic adrenalectomy is the preferred procedure for lesions smaller than 8 cm. If the pheochromocytoma is intra-adrenal, the standard approach is to remove the entire adrenal gland. In the case of a malignant pheochromocytoma, resect as much of the tumor as possible

CUSHING'S SYNDROME

Cushing syndrome is caused by prolonged exposure to elevated levels of either endogenous glucocorticoids or exogenous glucocorticoids. Endogenous glucocorticoid overproduction or hypercortisolism that is independent of ACTH is usually due to a primary adrenocortical neoplasm (usually an adenoma but rarely a carcinoma). Bilateral micronodular hyperplasia and macronodular hyperplasia are rare causes of Cushing syndrome.

Diagnosis

Obesity

Patients may have increased adipose tissue in the face (moon facies), upper back at the base of neck (buffalo hump), and above the clavicles (supraclavicular fat pads). Central obesity with increased adipose tissue in the mediastinum and peritoneum; increased waist-to-hip ratio greater than 1 in men and 0.8 in women; and, upon CT scan of the abdomen, increased visceral fat is evident.

Skin

Facial plethora may be present, especially over the cheeks. Violaceous striae, often wider than 0.5 cm, are observed most commonly over the abdomen, buttocks, lower back, upper thighs, upper arms, and breasts. Ecchymoses may be present. Patients may have telangiectasias and purpura. Cutaneous atrophy with exposure of subcutaneous vasculature tissue and tenting of skin may be evident.

Cardiovascular and renal

Hypertension and possibly edema may be present due to cortisol activation of the mineralocorticoid receptor leading to sodium and water retention.

Gastroenterologic

Peptic ulceration may occur with or without symptoms. Particularly at risk are patients given high doses of glucocorticoids (rare in endogenous hypercortisolism).

Endocrine

Galactorrhea may occur when anterior pituitary tumors compress the pituitary stalk, leading to elevated prolactin levels. Signs of hypothyroidism, such as slow reflex relaxation, may occur from an anterior pituitary tumor whose size interferes with proper thyroid-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) function. Similarly, other pituitary function may be interrupted. Low testosterone levels in men may lead to decreased testicular volume from inhibition of LHRH and LH/FSH function.

Skeletal/muscular

Proximal muscle weakness may be evident. Osteoporosis may lead to incident fractures and kyphosis, height loss, and axial skeletal bone pain. Avascular necrosis of the hip is also possible from glucocorticoid excess.

Neuropsychological

Patients may experience emotional liability, fatigue, and depression. Visual-field defects, often bitemporal, and blurred vision may occur in individuals with large ACTH-producing pituitary tumors that impinge on the optic chiasma.

Adrenal crisis

Patients with cushingoid features may present to the emergency department in adrenal crisis. Adrenal crisis may occur in patients on steroids who stop taking their glucocorticoids or neglect to increase their steroids during an acute illness. It also may occur in patients who have recently undergone resection of an ACTH-producing or cortisol-producing tumor or who are taking adrenal steroid inhibitors. Physical findings that occur in a patient in adrenal crisis include hypotension, abdominal pain, vomiting, and mental confusion (secondary to low serum sodium or hypotension). Other findings include hypoglycemia, hyperkalemia, hyponatremia, and metabolic acidosis.

Causes

Exogenous steroid administration

- Administration of exogenous steroids may lead to the development of Cushing syndrome.
- Symptoms of glucocorticoid excess generally occur with the administration of oral steroids; however, occasionally injections of steroids into joints and the use of steroid inhalers can cause Cushing syndrome.
- Patients with diseases that respond to steroid therapy are especially likely to receive steroids and thus develop Cushing syndrome. Such disorders include a wide variety of rheumatologic, pulmonary, neurological, and nephrologic diseases.
- Patients who have undergone organ transplants are also at risk for developing Cushing syndrome due to exogenous steroids required as part of graft antirejection medication regimens.

Endogenous glucocorticoid overproduction

1. ACTH-producing pituitary adenoma

- Pituitary adenomas that secrete ACTH are derived from corticotrophs in the anterior pituitary.
- ACTH secreted by corticotrophs is released into the circulation and acts on the adrenal cortex to produce hyperplasia and stimulate the secretion of adrenal steroids.
- These adenomas, if large, can result in loss of production of other anterior pituitary hormones (TSH, FSH, LH, growth hormone, and prolactin) and the posterior pituitary hormone vasopressin.
- Pituitary tumors can also compress the hypophyseal stalk leading to hyperprolactinemia from loss of dopamine inhibition.
- Nelson syndrome is caused by a large ACTH-secreting pituitary tumor; it is often locally invasive, difficult to cure, and associated with hyperpigmentation. In patients who undergo adrenalectomy without pituitary irradiation, the incidence of Nelson syndrome is about 20–25%.

2. Large pituitary adenomas may press on the optic chiasm, causing visual-field deficiencies that often present as bitemporal field cuts.

Tests may include increased 24-hour urinary free cortisol excretion in three separate collections, failure to appropriately suppress morning cortisol after overnight exposure to dexamethasone, and evidence of loss of diurnal cortisol secretion with high levels at midnight, the time of the physiologically lowest secretion. Factors potentially affecting the outcome of these diagnostic tests have to be excluded such as incomplete 24-hour urine collection or rapid inactivation of dexamethasone due to concurrent intake of CYP3A4-inducing drugs (e.g., antiepileptics, rifampicin).

Differential Diagnoses

Renal failure
Strenuous exercise
Phenobarbital
Phenytoin
Rifampin
Psychiatric illness

Differentiation of Cushing syndrome from pseudo–Cushing syndrome can sometimes be a challenge. A pseudo-Cushing state is defined as having some of the clinical features and biochemical evidence of Cushing syndrome. However, resolution of the primary condition results in disappearance of the cushingoid features and biochemical abnormalities.

In patients who chronically abuse alcohol, clinical and biochemical findings suggestive of Cushing syndrome are often encountered. Discontinuation of alcohol causes disappearance of these abnormalities, and, therefore, this syndrome is often specifically referred to as alcohol-induced pseudo-Cushing syndrome.

Patients with depression often have perturbation of the HPA axis, with abnormal cortisol hypersecretion. These patients rarely develop clinical Cushing syndrome. Because excess glucocorticoids can lead to emotional liability and depression, distinguishing between depression and mild Cushing syndrome is often a diagnostic challenge.

Tratment

Overt Cushing's is associated with a poor prognosis if left untreated. In ACTH-independent disease, treatment consists of surgical removal of the adrenal tumor. For smaller tumors, a minimally invasive approach can be employed, whereas for larger tumors and those suspected of malignancy, an open approach is preferred.

The remarkable anti-inflammatory properties of glucocorticoids have led to their use in a wide variety of clinical conditions, but the hazards are significant. Equivalent doses of commonly used glucocorticoids (Hydrocortisone: 20 mg, Cortisone acetate: 25 mg, Prednisolone: 5 mg, Dexamethasone: 0.5 mg). Topical preparations (dermal, rectal and inhaled) can also be absorbed into the systemic circulation. Although this rarely occurs to a sufficient degree to produce clinical features of Cushing's syndrome, it can result in significant suppression of endogenous ACTH and cortisol secretion.

VIRILIZING AND FEMINIZING ADRENAL TUMORS

Virilizing tumors of the adrenal gland are relatively rare entities not commonly seen in clinical practice. The estimated incidence is 1 per 1.7 million. Tumors of this type are rare and some are associated with adrenocortical carcinomas. A virilizing adrenal tumor makes excess androgens(testosterone). Patients often present with increased hair growth (hirsuitism), increased muscle mass, acne and amenorrhea (loss of periods in a female). A feminizing adrenal tumor makes excess estrogen. Patients often present with increased growth of breast tissue (gynecomastia/breast growth in men) and impotence in men.

Although hirsutism alone can be the initial presenting symptom, patients with an adrenal tumor usually present with other symptoms of virilization as well. Although more commonly observed in adults, the virilization usually manifest itself as excess facial and body hair, severe acne in the face and back areas, male pattern baldness, increased muscle mass and cliteromegaly. Reproductive age women will cease their menstrual periods as well. Symptoms of androgen excess however are not restricted to an adrenal tumor. Hyperandrogenism can present in patients with congenital adrenal hyperplasia and polycystic ovarian disease as well. Although rare, there is a bimodal peak in the age of incidence of virilizing adrenal tumors in the first and fourth decades of life.

Adrenal function testing is an important part of identifying the cause of excessive manifestations of virilism. Since congenital enzyme blocks are not that uncommon, the use of provocative adrenal function testing like the cortrosyn stimulation test is usual practice in working up a patient who presents

with signs and symptoms of androgen excess. The normal baseline levels of cortisol, 11 deoxycortisol and 17 hydroxy progesterone and response to exogenous ACTH tended to rule out an exzymatic block as the cause of excess androgen production. The key to the diagnosis was the DHEA-S level.

Treatment

Surgery was the only logical treatment choice for treating this isolated adrenal mass. Once the adrenal tumor was removed, the adrenal steroid pattern reverted to normal. It is expected that this young girl will experience normal puberty once the elevated androgen levels become normalized in her system.

CONGENITAL ADRENAL HYPERPLASIA

The term congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders, each of which involves a deficiency of an enzyme involved in the synthesis of cortisol, aldosterone, or both. Deficiency of 21-hydroxylase, resulting from mutations or deletions of CYP21A, is the most common form of CAH, accounting for more than 90% of cases.

Signs and symptoms

The clinical phenotype of CAH depends on the nature and severity of the enzyme deficiency. Although the presentation varies according to chromosomal sex, the sex of a neonate with CAH is often initially unclear because of genital ambiguity.

Clinical presentation in females

- Females with severe CAH due to deficiencies of 21-hydroxylase, 11-beta-hydroxylase, or 3-beta-hydroxysteroid dehydrogenase have ambiguous genitalia at birth (classic virilizing adrenal hyperplasia); genital anomalies range from complete fusion of the labioscrotal folds and a phallic urethra to clitoromegaly, partial fusion of the labioscrotal folds, or both
- Females with mild 21-hydroxylase deficiency are identified later in childhood because of precocious pubic hair, clitoromegaly, or both, often accompanied by accelerated growth and skeletal maturation (simple virilizing adrenal hyperplasia)
- Females with still milder deficiencies of 21-hydroxylase or 3-beta-hydroxysteroid dehydrogenase activity may present in adolescence or adulthood with oligomenorrhea, hirsutism, and/or infertility (nonclassic adrenal hyperplasia)
- Females with 17-hydroxylase deficiency appear phenotypically female at birth but do not develop breasts or menstruate in adolescence; they may present with hypertension

Clinical presentation in males

- Males with 21-hydroxylase deficiency have normal genitalia
- If the defect is severe and results in salt wasting, these male neonates present at age 1–4 weeks with failure to thrive, recurrent vomiting, dehydration, hypotension, hyponatremia, hyperkalemia, and shock (classic salt-wasting adrenal hyperplasia)

- Males with less severe deficiencies of 21-hydroxylase present later in childhood with early development of pubic hair, phallic enlargement, or both, accompanied by accelerated linear growth and advancement of skeletal maturation (simple virilizing adrenal hyperplasia)
- Males with steroidogenic acute regulatory (StAR) deficiency, classic 3-beta-hydroxysteroid dehydrogenase deficiency, or 17-hydroxylase deficiency generally have ambiguous genitalia or female genitalia; they may be raised as girls and seek medical attention later in life because of hypertension or a lack of breast development

Other findings
- Patients with aldosterone deficiency of any etiology may present with dehydration, hyponatremia, and hyperkalemia, especially with the stress of illness
- Males or females with 11-hydroxylase deficiency may present in the second or third week of life with a salt-losing crisis; later in life, these patients develop hypertension, hypokalemic alkalosis, or both
- Infants with StAR deficiency (lipoid adrenal hyperplasia) usually have signs of adrenal insufficiency (eg, poor feeding, vomiting, dehydration, hypotension, hyponatremia, hyperkalemia)
- Hyperpigmentation: Occurs in patients with deficiencies of enzyme activity involved in cortisol synthesis; may be subtle and is best observed in the genitalia and areolae

Diagnosis

The diagnosis of CAH depends on the demonstration of inadequate production of cortisol, aldosterone, or both in the presence of accumulation of excess concentrations of precursor hormones, as follows:
- 21-hydroxylase deficiency: High serum concentration of 17-hydroxyprogesterone (usually >1000 ng/dL) and urinary pregnanetriol (metabolite of 17-hydroxyprogesterone) in the presence of clinical features suggestive of the disease; 24-hour urinary 17-ketosteroid levels are elevated
- 11-beta-hydroxylase deficiency: Excess serum concentrations of 11-deoxycortisol and deoxycorticosterone, or an elevation in the ratio of 24-hour urinary tetrahydrocompound S (metabolite of 11-deoxycortisol) to tetrahydrocompound F (metabolite of cortisol); 24-hour urinary 17-ketosteroid levels are elevated
- 3-beta-hydroxysteroid dehydrogenase deficiency: An abnormal ratio of 17-hydroxypregnenolone to 17-hydroxyprogesterone and of dehydroepiandrosterone to androstenedione
- Salt-wasting forms of CAH: Low serum aldosterone concentrations, hyponatremia, hyperkalemia, and elevated plasma renin activity (PRA), indicating hypovolemia

- Hypertensive forms of adrenal hyperplasia (ie, 11-beta-hydroxylase deficiency and 17-alpha-hydroxylase deficiency) are associated with suppressed PRA and, often, hypokalemia
- Subtle forms of adrenal hyperplasia (as in nonclassic forms of 21-hydroxylase deficiency and nonclassic 3-beta-hydroxysteroid dehydrogenase deficiency): Synthetic corticotropin (Cortrosyn) stimulation testing demonstrates the abnormal accumulation of precursor steroids; nomograms are available for interpreting the results

Imaging studies
- CT scanning of the adrenal gland can help exclude bilateral adrenal hemorrhage in patients with signs of acute adrenal failure without ambiguous genitalia or other clues to adrenal hyperplasia
- Pelvic ultrasonography may be performed in an infant with ambiguous genitalia to demonstrate a uterus or associated renal anomalies, which are sometimes found in other conditions that may result in ambiguous genitalia (eg, mixed gonadal dysgenesis, Denys-Drash syndrome)
- Urogenitography is often helpful in defining the anatomy of the internal genitalia
- A bone-age study is useful in evaluating for advanced skeletal maturation in a child who develops precocious pubic hair, clitoromegaly, or accelerated linear growth

Other tests
- A karyotype is essential in an infant with ambiguous genitalia, to establish the chromosomal sex
- Genetic testing is essential for genetic counseling and prenatal diagnosis of adrenal hyperplasia
- Newborn screening programs for 21-hydroxylase deficiency may be lifesaving in an affected male infant who would otherwise be undetected until presentation with a salt-wasting crisis

Treatment
The Endocrine Society's 2010 clinical practice guidelines note the following:
- Prenatal treatment for CAH should be regarded as experimental.
- Glucocorticoid therapy should be carefully titrated to avoid Cushing syndrome.
- Mineralocorticoid replacement is encouraged. In infants, mineralo-corticoid replacement and sodium supplementation are encouraged.
- Use of agents to delay puberty and promote growth are experimental.
- Psychiatric support should be encouraged for patients with adjustment problems.
- Medication should be used judiciously during pregnancy and in symptomatic patients with nonclassical CAH.

Patients with dehydration, hyponatremia, or hyperkalemia and a possible salt-wasting form of adrenal hyperplasia should receive an intravenous (IV) bolus of isotonic sodium chloride solution (20 mL/kg or 450 mL/m^2) over the

first hour, as needed, to restore their intravascular volume and blood pressure. This dosage may be repeated if the blood pressure remains low.

Dextrose must be administered if the patient is hypoglycemic and must be included in the rehydration fluid after the bolus dose to prevent hypoglycemia. After samples are obtained to measure electrolyte, blood sugar, cortisol, aldosterone, and 17-hydroxyprogesterone concentrations, the patient should be treated with glucocorticoids based on suspected adrenal insufficiency. Treatment should not be withheld while confirmatory results are awaited because it may be life preserving.

After the patient's condition is stabilized, treat all patients who have adrenal hyperplasia with long-term glucocorticoid or aldosterone replacement (or both), depending on which enzyme is involved and on whether cortisol and/or aldosterone synthesis is affected.

Another approach currently under investigation is the combined use of glucocorticoid (to suppress ACTH and adrenal androgen production), mineralo-corticoid (to reduce angiotensin II concentrations), aromatase inhibitor (to slow skeletal maturation), and flutamide (an androgen blocker to reduce virilization).

Some patients develop precocious puberty, which further compromises adult height. Suppression of puberty with long-acting gonadotropin-releasing hormone (GnRH) agonists while simultaneously stimulating growth with growth hormone may partially improve the patient's height.

Control of initial level of knowledge

1. The diagnosis of insufficiency of 21-hydroxylasa patient with a adrenogenital syndrome is confirmed by all indicated indexes, except:

A. *Increase the excretion of 17 CS with urine.*
B. *Increase the level of 11-desoxycorticosterone in plasma.*
C. *Increase the level of 17-hydroxyprogesterone in plasma.*
D. *Increase the level of androstendione in plasma.*
E. *Increase the excretion with urine of pregnandiol and pregnantriol.*

2. From transferred measures transfer those which are not necessary for the patient with Addison's crisis

A. *Infusion the isotonic solution of sodium chloride.*
B. *Infusion the hypotonic solution of sodium chloride.*
C. *Infusion the solution of glucose.*

3. During the leadthrough of substitute therapy at hypercorticism what time is it better to appoint the evening reception of glucocorticosteroids?

A. *Before sleeping.*   B. *In the evening.*   C. *Till 6 p.m.*

4. From the resulted clinical signs of hyporeninaemic hypoaldosteronism isnot :

A. *Hyperkaliemia.*   D. *Muscle cramps.*
B. *Muscular weakness.*   E. *Signs of kidney insufficiency.*
C. *Abnormal heart rhythm.*

34

5. How does the secretion of aldosterone change in patients with a hypercorticoidism?

A. Rises.   B. Goes down.   C. Stay within the limits of norm.

6. What day's dose of dexamethasone does use for the conducting of "small" dexamethasone test for diagnostics of Cushing`s syndrome?

A. 1 mg.   B. 2 mg.   C. 4 mg.   D. 8 mg.   E. 16 mg.

7. The Conn's syndrome is characterised by:

A. Oliguria.   B. Polyuria.   C. Pollackiuria.   D. Nicturia.

8. What level of active renin in plasma at the secondhyperaldosteronism?

A. Increased.   B. Depressed.   C. Stay without the changes.

9. At presence of androsteroma at boys arises up:

A. Real isosexual premature sexual ripening.

B. Unreal isosexual premature sexual ripening.

C. Unreal heterosexual sexual ripening.

10. What preparations are contra-indicated at treatment of Addison's disease?

A. Prednisolone.   C. ACTH.

B. Desoxycorticosteroni acetas.   D. Dexamethasone.

Correct answers:

1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
B	B	C	D	C	B	B	A	B	C

Control of final level of knowledge

1. The low doses of adrenalin cause the following change in the function of the cardiac system, except :

A. Increase the minute volume of heart.

B. Reduce peripheral resistance of vessels.

C. Increase peripheral resistance of vessels.

D. Activate β-receptors of vessels and heart.

2. What do catecholamins do toward the exchange of carbohydrates?

A. Activation of hepatin synthesis.

B. Activation of gluconeogenesis.

C. Activation of glucose metabolism intissues.

D. Activation of glucose transport.

3. How do catecholamins influence on the exchange of lipids?

A. Stimulate synthesis of fat acids.

B. Activate processes of lipogenesis.

C. Stimulate processes of adipocitis differentiation.

D. Stimulate lipolise in fat tissue.

4. How do catecholamins influence on the exchange of sodium in an organism?

A. Increase the excretion.   C. Increase the reabsorbtion.

B. Reduce the reabsorbtion.   D. Does not influence on exchange of sodium.

5. How do catecholamins influence on the exchange of calcium in an organism?

A. *Increase the level of calcium in plasma of blood.*

B. *Reduce the level of calcium in plasma of blood.*

C. *Increase excretion of calcium with urine.*

D. *Does not influence on exchange of calcium.*

6. What medicinal preparation should not be prescribed to a patient with feochromocitoma?

A. *Ganglioplegics.*   C. *β-adrenoplegics.*

B. *α-adrenoplegics.*   D. *Chloditane.*

7. What electrolytes of blood does change during test with spironolactone at diagnostics of Conn's syndrome?

A. *Increase the level of sodium.*   C. *Increase the level of potassium.*

B. *Reduce the level of potassium.*   D. *Reduce the level of sodium.*

8. What differences in the level of hormones between primary hypercorticism from the second?

A. *Low level of glucocorticoids and the normal level of mineralcorticoids.*

B. *Low level of gluco-and mineralcorticoids.*

C. *Normal level of glucocorticoids and mineralcorticoids.*

9. How the level of aldosterone will change in reply to loading by the chloride of sodium at presence of Conn`s syndrome?

A. *Reduce to 50% and below.*   C. *Stay without the changes.*

B. *Will rise.*   D. *Reduce less than on 50%.*

10. What metabolic complications is often observed in patients after excision of pheochromocytoma?

A. *Level of calcium in the whey of blood.*   D. *Lipidemia.*

B. *Violation the balance of electrolytes.*   E. *Glucopenia.*

C. *Change the level of potassium in a blood.*

Correct answers:

1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
C	B	D	C	A	D	C	B	D	E

Situational tasks

1. A man, 36 years old presents. He had expressed weakness, bad appetite, nausea during 1–1.5 years. Weight lossfor 1 year on 10 kg. The skin of face, neck, overhead is dark. Considerable pigmentation of skin folds, nipples. Pulse – 60/min. Blood pressure 80/50 mm. Previous diagnosis?

A. *Chronic gastritis.*   D. *Chronic hepatitis.*

B. *Cushing's disease.*   E. *Insufficiency of glands.*

C. *Diabetes mellitus.*

2. A woman, 42 years old presents with complaints: periodic squeezing pain in the region of heart, expressed weakness at proximal muscles on extremities and cramp, pain in the back of head. Height 176 см, mass of body is 80 kg. The lines of heart are displaced to the left. EKG: sine rhythm, obliquely-descending decline of ST segment. Pulse – 92/min. Arterial pressure is 190/100 мм. Polyuria, nycturia with isosthenuria. Hyporeninaemia. Potassium – 2,8 mmol/l. What is the credible diagnosis?

A. Primary aldosteronism.　　　　　*D. Feochromocitoma.*
B. Hyperparathyreoidism.　　　　　*E. Cushing's syndrome.*
C. Essential hypertension.

3. A boy 7 years is hospitalized with the complaints of parents about speed-up physical and prematuresexual development. After the inspection the diagnosis of adrenogenital syndrome, virile is set. What is appointed for substitutetherapy?

A. Prednisolone.　　　*C. Cortinef.*　　　　*E. Vitamins A, E.*
B. Fluorinef.　　　　　*D. DOCSA.*

4. A man 32 years old, complains for a year about a weakness in muscles, thirst, polyuria, and headache. Height is 180 см, mass of body – 76 kg, ps – 76/min, arterial blood pressure – 170/105 mmHg Skin of ordinary color. The edema are absent. Hypopotassiumaemia, hypernatremia, hypochloraemia. Relative density of urine – 1007, reaction alkaline, proteinuria – 0,033 g/l. Diagnosis?

A. Konn`s syndrome.　　　　　*C. Glomerulonephritis.*
B. Hyperparathyreosis.　　　　　*Д. Cushing`s syndrome.*

5. A woman, 27 years old, with the satisfactorily compensated diabetes mellitus, type 1, complains about frequent glucopenias, nausea, disorders of intestine, arterial blood pressure diminished to 80/50 mm. Anaemia, НЬ – 105 g/l. What can predefine the decline of pressure?

A. Diabetic enteropathy.
B. Diabetic gastropathy.
C. Chronic insufficiency of adrenal glands.
D. Overdose of antidiabetic preparations.
E. Unsaccharine diabetes.

6. A man 28 years old complains about pain in a lumbar area with an irradiation in a left leg. Objectively: is 186 cm, weight is 92 kg. Blood pressure – 170/100 мм. Pulse – 84/min. It is present purple striae on a stomach and thighs. On a X-ray osteoporosis, compression break of L-IV. In a blood: Er – $5.5×10^{12}$/l, НЬ –190 g/l, leuc – $9×10^{12}$ л· Calcium – 3,3 mmol/l. What most probable cause of break?

A. Constitutional obesity.　　　　*D. Primary hyperparathyroidism.*
B. Trauma.　　　　　　　　　　　*E. Cushing`s syndrome.*
C. Polycitaemia.

7. Brothers 7 and 5 years old, hospitalized in connection with the complaints of parents about speed-up physical and premature sexual development. After the inspection a diagnosis is set: adrenogenital syndrome, virile, form. What preparation does appoint?

    A. DOCSA.   *C. Cortinef.*   *E. Vitamins A, E.*
    B. Fluorinef.   *D. Prednisolone.*

8. Woman 39 years old, complains about headache, weakness and paresthesias in extremities, polyuria. Objectively: tones of heart are muffled, ps – 94/min, blood pressure – 105/90 мм. Glucose of blood 5,5 mmol/l, sodium of plasma – 148 g/l, potassium of plasma – 2,7 mmol/l. relative density – 1012, albumen is reaction alkaline, leuc – 3–4. The most probablediagnosis:

    A. Hypertonic disease.   *D. Chronic glomerulonephritis.*
    B. Amyloidosis.   *E. Primary hyperaldosteronism.*
    C. Diabetes mellitus.

9. Endocrinologist was quickly caused to the urology clinic to sick, 46 years old, which was hospitalized with the attack of kidney colic**.** During the instrumental inspection a patient lost consciousness. The arterial blood pressure went down to 40/20 mm. In anamnesis the protracted (6 years) reception of glucocorticoids in connection with a pseudorheumatism. Halted the reception of glucocorticoids 3 days ago. Objectively: tones of heart deaf, pulse – 100/min, weak filling, rhythmic. Lights and organs of abdominal region without features. Diagnosis?

    A. Addison's crisis.   *D. Cushing's syndrome.*
    B. Adrenogenital syndrome.   *E. Allergic shock.*
    C. Acute adrenal insufficiency.

10. A woman, 32 years old, is ill 8 month and complains about a weakness in muscles, periodic cramps, attacks of acute general weakness, polyuria, and nycturia. Tones of heart are muffled, accent II of tone above an aorta, blood pressure is 170/100 mm. In a blood: potassium – 3,0 mmol/l, glucose – 5,3 mmol/l. In the general analysis of urine: alkalireaction of urine, albumen – 0,066 g/l, leuc – 3–5, hipoisosthenuria. Diagnosis?

    A. Primary hyperaldosteronism.   *D. Cushing's syndrome.*
    B. Hypertonic disease.   *E. Feochromocitoma.*
    C. Chronic pyelonephritis.

Correct answers:

1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
E	A	A	A	C	E	D	E	C	A

Controls questions

1. Acute insufficiency of adrenal glands: ethiology, patogenesis, clinic and treatment.
2. Chronic insufficiency of adrenal glands cortex: etiology, pathogenesis.
3. Classification of chronic insufficiency of adrenal glands.
4. Basic diagnostic signs of Addison's disease.
5. Differential diagnosis of Addison's disease.
6. Differential diagnosis of primary and secondary hypocorticism.
7. Treatment of chronic insufficiency of adrenal glands.
8. Addison's crisis: ethiopathogeny, clinic, treatment.
9. Corticosteroma: pathogenic, clinical displays, treatment.
10. Signs of Cushing's syndrome.
11. Differential diagnosis and treatment of Cushing's syndrome.
12. Conn`s syndrome. Ddiagnostic signs.
13. Primary aldosteronism: differential diagnosis, treatment.
14. Virilizing and Feminizing Adrenal Tumors. D, basic diagnosis criteria.
15. Differential diagnostics and treatment of Virilizing Adrenal Tumors.
16. Pheochromocytoma: , classification.
17. M diagnostic signs of pheochromocytoma
18. Differential diagnostics and treatment of pheochromocytoma.
19. Congenital adrenal hyperplasia. Ethiology, pathogenesis, classification.
20. Basic diagnostic signs of congenital adrenal hyperplasia.
21. Differential diagnosis and treatment of congenital adrenal hyperplasia.

FURTHER READING:

1. Davidson's Principles and Practice of Medicine. / ed. by Nicki R. Colledge. – Elsevier press. –Twenty-first edition, 2010. – 1377 p.
2. Harrison's Principles of Internal medicine (18th edition). – 2011. – 4322 p.
3. Endocrinology and metabolism / Ed. by Pincher. – London : McGraw Hill Int., 2001. – 811 p.
4. Handbook of Physiology. Section 7: Endocrine system. Volume III: Endocrine regulation of Water and electrolyte balance / ed. by J. C. S. Fray. – Oxford University press, 2000. – 750 p.
5. Textbook of endocrine physiology / ed. by J .E. Griffin, S. R. Ojeda. – 4-Th ed. – Oxford University press, 2000. – 490 p.
6. Endocrinology and metabolism / ed. by Pinchera. – London : McGraw Hill Int., 2001. – 811 p.
7. Ladenson P., Kim M. Thyroid. In: Goldman L and Ausiello D, eds. *Cecil Medicine*. 23rd ed. Philadelphia, Pa: Saunders; 2007: chap 244.

Навчальне видання

ЗАХВОРЮВАННЯ ЕНДОКРИННОЇ СИСТЕМИ. ХРОНІЧНА НЕДОСТАТНІСТЬ КОРИ НАДНИРКОВИХ ЗАЛОЗ. ЕТІОЛОГІЯ, ПАТОГЕНЕЗ, КЛІНІКА, ДІАГНОСТИКА, ПРОФІЛАКТИКА ТА ЛІКУВАННЯ. ГОСТРА НЕДОСТАТНІСТЬ КОРИ НАДНИРКОВИХ ЗАЛОЗ. ГОРМОНАЛЬНО-АКТИВНІ ПУХЛИНИ НАДНИРКОВИХ ЗАЛОЗ

Методичні вказівки
для студентів IV курсу

Упорядники   Журавльова Лариса Володимирівна
                Федоров Володимир Олександрович
                Філоненко Марина В'ячеславівна
                Янкевич Олександр Олександрович
                Кривоносова Олена Михайлівна
                Олійник Марія Олександрівна

Комп'ютерна верстка О.Ю. Лавриненко

DISEASES OF ENDOCRINE SYSTEM. CHRONIC INSUFFICIENCY OF ADRENAL CORTEX GLANDS. ETIOLOGY, PATHOGENESIS, CLINICAL PRESENTATION, DIAGNOSIS, PREVENTION AND TREATMENT. ACUTE INSUFFICIENCY OF ADRENAL CORTEX GLANDS. HORMONAL-ACTIVE TUMORS OF ADRENAL GLANDS

*Methodological recommendations
for students of IV course*