N. O. Kravchun, P. P. Kravchun, U. S. Herasymchuk

CHRONIC ADRENAL INSUFFICIENCY: PATHOGENESIS, CLINICAL PRESENTATION, DIAGNOSIS, TREATMENT APPROACHES

Self-study manual
for students, participants of refreshment courses
and endocrinologists

МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
Харківський національний медичний університет

N. O. Kravchun, P. P. Kravchun, U. S. Herasymchuk

CHRONIC ADRENAL INSUFFICIENCY: PATHOGENESIS, CLINICAL PRESENTATION, DIAGNOSIS, TREATMENT APPROACHES

Self-study manual
for students, participants of refreshment courses
and endocrinologists

Н. О. Кравчун, П. П. Кравчун, У. С. Герасимчук

ХРОНІЧНА НАДНИРКОВА НЕДОСТАТНІСТЬ: ПАТОГЕНЕЗ, КЛІНІКА, ДІАГНОСТИКА, ПІДХОДИ ДО ЛІКУВАННЯ

Навчальний посібник
для самостійної роботи здобувачів вищої освіти,
слухачів курсів післядипломної освіти
та лікарів-ендокринологів

Харків
ХНМУ
2024

УДК 616.45-008.64-036.12-092-07-085-035
К81

Затверджено Вченою радою ХНМУ.
Протокол № 5 від 23.05.2024.

Автори: Кравчун Н. О., Кравчун П. П., Герасимчук У. С.

Рецензенти:

Місюра К. В. – д-р мед.н., професорка (директорка ДУ «Інститут проблем ендокринної патології ім В.Я. Данилевського НАМН України»).

Рудик Ю. С. – д-р мед.н., професор (завідувач відділу клінічної фармакології та фармакогенетики неінфекційних захворювань ДУ «Національний інститут терапії ім. Л. Т. Малої України»).

К81 Хронічна надниркова недостатність: патогенез, клініка, діагностика, підходи до лікування: навч. пос. для самостійної роботи здобувачів вищої освіти, слухачів курсів післядипломної освіти та лікарів-ендокринологів / Н. О. Кравчун, П. П. Кравчун, У. С. Герасимчук. Харків : ХНМУ, 2024. 64 с.

У навчальному посібнику детально викладено сучасні уявлення щодо епідеміології, етіопатогенезу, клінічного перебігу, діагностики, диференційної діагностики, підходів до лікування, профілактики та прогнозу хронічної надниркової недостатності. Висвітлені матеріали будуть корисними для самостійної роботи здобувачів вищої освіти, слухачів курсів післядипломної освіти та лікарів-ендокринологів. Представлені питання для контролю рівня знань та клінічні ситуаційні завдання.

УДК 616.45-008.64-036.12-092-07-085-035

© Харківський національний медичний університет, 2024
© Кравчун Н. О., Кравчун П. П., Герасимчук У. С., ХНМУ, 2024

UDC 616.45-008.64-036.12-092-07-085-035
K81

Approved by the Academic Council of the KNMU.
Protocol № 5 dated 23.05.2024.

Editors: Kravchun N. O., Kravchun P. P., Herasymchuk U. S.

Reviewers:

Misyura K. V. – doctor of medical sciences, professor (director State Institution «V. Danilevsky Institute for Endocrine Pathology Problems of the National Academy of Medical Sciences of Ukraine»).

***Rudyk I. S*.** – doctor of medical sciences, professor (head of department of clinical pharmacology and pharmacogenetics of non-infectious disease Government Institution «L. T. Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine»).

K81 Chronic adrenal insufficiency: pathogenesis, clinical presentation, diagnosis, treatment approaches: self-study manual for students, participants of refreshment courses and endocrinologists / editors **N. O.** Kravchun, P. P. Kravchun, U. S. Herasymchuk. Kharkiv : KNMU, 2024. 64 p.

This manual describes in detail the modern concepts of epidemiology, etiopathogenesis, clinical course, diagnosis, differential diagnosis, treatment approaches, prevention, and prognosis of chronic adrenal insufficiency. The presented materials will be useful for self-study of the students of higher education, participants of refreshment courses and endocrinologists. Questions to control the level of knowledge and clinical situational tasks are presented.

UDC 616.45-008.64-036.12-092-07-085-035

© Kharkiv National Medical University, 2024
© Kravchun N. O., Kravchun P. P., Herasymchuk U. S., KNMU, 2024

Contents

List of abbreviations 3
The issue of primary control of knowledge 4
Historical background 4
Primary chronic adrenal insufficiency 6
Hypocorticism of central origin 28
Adrenal insufficiency in children 33
Hypocorticism and pregnancy 35
Genetic syndromes accompanied by hypocorticism 39
Autoimmune polyendocrine (polyglandular) syndromes 41
Congenital hypoplasia of the adrenal cortex 45
ACTH synthesis defect 46
Hypoaldosteronism 48
Acute adrenal insufficiency 52
Tests 60
Correct answers 61
References 62

LIST OF ABBREVIATIONS

AAI – Acute adrenal insufficiency
ACTH – Adrenocorticotropic hormone
APS – Autoimmune polyglandular syndrome
BP – Blood pressure
CAI – Chronic adrenal insufficiency
CRH – Corticotropin-releasing hormone
CT scans – Computed tomography
DOCA – Deoxycorticosterone acetate
GCs – Glucocorticoids
LCFAs – Long-chain fatty acids
MRI scans – Magnetic resonance imaging
PsHA – Pseudohypoaldosteronism
TSH – Thyroid-stimulating hormone

THE ISSUE OF PRIMARY CONTROL OF KNOWLEDGE

1. Who was the first to describe the «bronze skin» symptom complex?
2. What types of chronic adrenal insufficiency are distinguished depending on the localization of the pathological process?
3. List the diseases that can lead to the development of primary chronic adrenal insufficiency?
4. What clinical manifestations are characteristic of primary chronic adrenal insufficiency?
5. List the mechanisms of action of corticosteroids.
6. What are the drugs for hormone replacement therapy?
7. What genetic syndromes can be accompanied by hypocorticism?
8. Define the term «acute adrenal insufficiency».
9. Provide a clinical description of the stages of acute adrenal insufficiency.
10. What are the therapeutic tactics of acute adrenal insufficiency?

HISTORICAL BACKGROUND

In 1855, T. Addison described a clinical symptom complex that he called «bronze skin»; even then this disease was associated with damage to the adrenal glands. In his work, T. Addison indicated that back in 1831, R. Bright reported a similar case of the disease with a fairly accurate presentation of clinical data. T. Addison not only gave a detailed description of the clinical picture of the disease observed in 11 patients, but also presented the results of the autopsy, which showed that the causes of damage to the adrenal glands were: tuberculosis, tumor metastases and atrophic changes - caused, according to the author, by a previous inflammatory process.

T. Addison's message served as an incentive for the research aimed at developing methods of replacement therapy for patients with destructive changes in the adrenal glands. By 1903, 97 cases of Addison's disease were described in the literature using organotherapy in the form of dried whole adrenal gland, dry extract, aqueous, alcoholic and glycerin extracts, which were administered enterally and parenterally, and stable improvement was observed in 16 of the described patients. In one of them, observed by W. Osler in 1896, a glycerol extract of fresh sheep adrenal glands was particularly effective both enterally and subcutaneously. With the cessation of taking this extract, the patient developed acute adrenal insufficiency, which was fatal.

For a long time, attempts to prepare adrenal cortex extracts for the treatment of patients with Addison's disease remained unsuccessful because the extracts were crude, with very limited efficiency. After the isolation of adrenaline in 1901, further attempts to isolate hormones from the adrenal cortex ceased until the 1920s.

In 1927, M. Rogoff and G. N. Stewart, F. A. Hartman et al., and in 1929, J. J. Pfiffner and W. W. Single were able to extend the lifespan of adrenalectomized animals using adrenal gland extract. Its use in the treatment of patients with Addison's

disease and the positive results obtained stimulated interest both in attempts to fractionate adrenal extracts and in the production of synthetic adrenal hormones.

The important stages of the research were:

• isolation in 1936 from an extract of the bovine adrenal gland of «compound E», called cortisone;

• carried out in 1937: synthesis of 11-deoxycorticosterone from stigmasterol and isolation of «substance F» from the adrenal glands, identical to «compound E».

In 1940, 17β-oxyprogesterone and 17-oxy-11-deoxycorticosterone, or «compound S», were isolated from the adrenal cortex. The amorphous residue remaining after extraction of crystalline fractions from the adrenal cortex extract retained high physiological activity. In 1952-1953 the active principle of this amorphous residue – «aldosterone», was isolated, which was soon chemically identified as Δ^4-pregnen-11β, 21-diol-3,20-dione-18-al. The synthesis of cortisone in 1946 and clinical evaluation of its anti-inflammatory effect in rheumatoid arthritis was a significant achievement.

For the research into the clinical use of cortisone in patients with rheumatoid arthritis, a group of scientists was awarded the Nobel Prize in 1950.

In 1953, fludrocortisone was synthesized, comparable in its mineralocorticoid effect to aldosterone. The new drug replaced deoxycorticosterone acetate (DOCA), whose biological activity is 30 times less than aldosterone.

Soon after the synthesis of prednisone and prednisolone in 1955, other corticosteroids were synthesized.

In the 20s of the twentieth century, the influence of the pituitary gland on the functional state of the adrenal cortex was proven. In support of this discovery, in 1943, a group of scientists – Li C. H., Simpson M. E., Evans H. M. – isolated adrenocorticotropic hormone (ACTH) in sheep. The synthesis of corticotropin was carried out in 1966. The mechanism of regulation of ACTH secretion by the pituitary gland using corticotropin-releasing hormone (CRH) was described in the 40s of the last century, and the establishment of the structure of CRH and its synthesis was carried out in the laboratory of Vale W. in 1981.

Definition, terminology, classification

The term «hypocorticism» (synonymous – adrenal insufficiency) combines a large group of diseases based on a decrease in the production of corticosteroids as a result of damage to one or more parts of the hypothalamic-pituitary-adrenal cortex system. Depending on the rate of development of clinical symptoms, chronic and acute adrenal insufficiency are distinguished.

Based on the localization of the pathological process, the following are distinguished:

– primary chronic adrenal insufficiency (CAI) (primary CAI) – a consequence of a destructive process in which more than 90 % of the cells of the adrenal cortex are destroyed;

– secondary CAI associated with a decrease or absence of ACTH secretion by the pituitary gland;

– tertiary CAI, developing as a result of damage to the hypothalamus, leading to corticoliberin deficiency.

PRIMARY CHRONIC ADRENAL INSUFFICIENCY

Prevalence. Primary CAI – is a relatively rare disease; the frequency of new cases ranges from 40–60 to 100–110 per 1 million adults per year. The manifestation of the disease is more often observed at 30–40 years of age; the ratio of men and women suffering from primary CAI is 2 : 1.

Etiological factors

For many years, tuberculosis was considered as the most common cause of primary damage to the adrenal cortex. I. B. Khavin in 1955 observed tuberculosis of the adrenal glands in 12 of 15 sectional cases of Addison's disease. According to G. S. Zefirova (1963), in 64 out of 100 patients, Addison's disease was associated with adrenal tuberculosis, while changes of tuberculous nature were observed in the lungs, bones, and abdominal lymph glands. Damage to the adrenal cortex in the active form of tuberculosis is a consequence of hematogenous dissemination of the infection, while clinical signs of tuberculosis of extra-adrenal localization may be absent. Destruction of the adrenal cortex associated with tuberculous lesions develops gradually; the brain part is often involved in the pathological process. In the early stages of the disease, an increase in the size of the adrenal gland is noted due to inflammatory infiltration and the formation of granulomas, but later fibrosis develops and the granulomas are replaced by caseous nodes, which is accompanied by a decrease in its size.

Currently, tuberculosis of the adrenal glands is not considered as the leading cause of Addison's disease, but it must be taken into account that in our country in recent years there has been a tendency to increase the prevalence of tuberculosis infection.

In the 60s of the last century, antibodies to the components of the adrenal cortex tissue were first discovered in the blood of patients with the so-called «idiopathic» form of primary CAI. In recent decades, there has been an increase in autoimmune damage to the adrenal cortex. In foreign literature, primary CAI is described under the name «autoimmune Addison's disease»; autoimmune adrenalitis is considered as the main cause of the development of the disease.

The pathogenetic mechanisms of primary CAI of autoimmune origin are largely identical to those observed in other organ-specific autoimmune diseases. Normally, T and B lymphocytes differentiate from bone marrow stem cells; subsequently, in the thymus, autoreactive thymocytes die through apoptosis. The development of primary CAI is due to the fact that, under the influence of genetic and exogenous factors, T cells that react with the own adrenal cortex enter the peripheral

bloodstream, where they recognize their specific auto-antigens, which causes destructive changes in the adrenal tissue. In addition, T cells stimulate autoreactive B cells, which begin to produce specific autoantibodies. At the same time, intense lymphoid infiltration is detected in the adrenal cortex, the amount of fibrous tissue increases – with pronounced atrophy of functional cells. Antibodies to microsomal and mitochondrial antigens of adrenal cortex cells are detected in the blood serum of such patients.

It has been established that the «target» for antibodies in Addison's disease is the key enzyme of adrenal steroidogenesis – 21-hydroxylase. Localized in the endoplasmic reticulum of adrenal cortex cells, this enzyme catalyzes the reaction in the zona fasciculata converting 17-hydroxyprogesterone into 11-deoxycortisol, -providing the synthesis of cortisol. 21-hydroxylase is also necessary for the conversion of progesterone to 11-deoxycorticosterone and the synthesis of aldosterone. The genes encoding 21-hydroxylase are located in the locus of class III histocompatibility antigens (MHC – Major Histocompatibility Complex, short arm of chromosome 6, TNF genes, HSP 70, C4, 21-OH). The connection of the disease with HLA antigens is evidenced by the detection of haplotypes DR3, DR4, AL, B8 in the majority of patients. The relative risk of the disease increases significantly in the presence of haplotypes DR3, DR4 and heterozygosity for these alleles, respectively.

Autoimmune damage to the adrenal cortex, accompanied by the development of primary CAI – is a significant component of autoimmune polyglandular syndrome (APS), adrenoleukodystrophy and other genetically determined diseases.

The causes of primary CAI can be: amyloidosis, hemochromatosis, syphilis, brucellosis; systemic mycoses – coccidioidomycosis, paracoccidioidomycosis, less often – candidiasis, blastomycosis, histoplasmosis, cryptococcosis. Among them, paracoccidioidomycosis (South American blastomycosis), common in Latin American countries, prevails. This fungal infection is characterized by primary damage to the lungs – with the development of granulomas surrounding the area of caseous necrosis or microabscesses, as well as lymph nodes of the mucous membrane of the oral cavity and upper respiratory tract.

Primary CAI occurs due to the influence of iatrogenic factors: the use of steroidogenesis blockers – chloditan, ketoconazole, aminoglutethimide; therapy with anticoagulants, spironolactone; performing a total adrenalectomy. The latter is carried out for patients with endogenous hypercortisolism of central origin – in case of severe disease or ineffectiveness of such treatment methods as adrenalectomy and radiation therapy. With total adrenalectomy, hypocorticism may be one of the components of Nelson's syndrome, the development of which is caused by a pituitary adenoma secreting ACTH. Symptoms of hypocorticism may appear a few days after hemorrhages in the adrenal glands with sharp pain in the lower back; sometimes they develop with sepsis, trauma, hypertension.

Subclinical adrenal insufficiency is often found in immunodeficiency syndrome (HIV infection). Clinical signs of adrenal insufficiency usually appear in the later stages of acquired immunodeficiency syndrome (AIDS). In this case, destructive changes in the adrenal tissue are caused by cytomegalovirus and fungal infections, Kaposi's sarcoma, lymphoma and other pathological processes. Metastatic damage to the adrenal glands, causing the development of clinically significant hypocorticism, can be observed in non-Hodgkin large cell lymphoma; somewhat less frequently, the disease is associated with metastases of bronchogenic lung cancer.

Primary hypocorticism – is a rare complication of antiphospholipid syndrome, developing as a result of bilateral thrombosis of the adrenal veins, as well as other coagulopathies that can lead to the development of hemorrhagic infarction of both adrenal glands – in particular, those associated with therapy with anticoagulants and antiplatelet agents.

Clinical symptoms and their pathogenesis

The frequency of occurrence of the main clinical manifestations of primary CAI and the observed electrolyte disturbances is presented in *Table 1*.

Table 1

Clinical signs of primary adrenal insufficiency (Endocrinology according to D. M. Williams)

Symptoms, signs, or laboratory findings	Frequency,%
Symptoms	
Weakness, fatigue, increased fatigability	100
Anorexia	100
Symptoms from the gastrointestinal tract	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salty cravings	16
Postural dizziness	12
Muscle or joint pain	6–13
Signs	
Weight loss	100
Hyperpigmentation	94
Hypertension (systolic BP < 110 mm Hg)	88–94
Vitiligo	10–20
Calcifications of the auriculars	5
Laboratory findings	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

The onset of clinical manifestations of primary CAI is observed with the destruction of at least 90 % of the volume of adrenal cortex tissue, which determines such a feature of the disease as its gradual onset and slow development. As T. Addison noted, the disease proceeds so slowly that «the patient can hardly remember the time of the first appearance of weakness, which is so short-lived that it is almost not felt». In addition to the «gradual course», the author pointed to «general weakness and asthenia, a sharp weakening of cardiac activity, increased susceptibility to the stomach and specific changes in skin color». Symptoms of primary CAI are pathogenetically caused by insufficient production of hormones that regulate metabolic processes; they are very numerous and varied, and the severity of each of them depends on the etiological factor, the duration of the disease and the severity of its course, on the individual characteristics of the patients.

Addison's disease, as a rule, manifests itself at the age of 30–40 years, and is more common in women, which is associated with the predominance of autoimmune disorders in them. Tuberculous etiology of the disease is observed with equal frequency in men and women.

The pathogenesis of the symptom complex of primary CAI is based on an absolute deficiency of corticosteroids. Moreover, especially severe metabolic changes are caused by a decrease in the production of mineralocorticoids, including aldosterone – as the most biologically active hormone. Insufficient production of glucocorticoids (GCs) in the adrenal cortex aggravates water-electrolyte changes associated with mineralocorticoid deficiency and causes severe disturbances in carbohydrate, protein and other types of metabolism:

– the processes of gluconeogenesis slow down significantly;

– glycogen reserves in muscles are depleted;

– relative hyperinsulinism develops, which is manifested by a decrease in blood glucose levels, a flat glycemic curve with a pronounced hypoglycemic phase.

– albumin synthesis in the liver is inhibited;

– anabolic processes in tissues are reduced, which is facilitated by insufficient synthesis of adrenal androgens;

– weight loss progresses.

Hyperkalemia, dehydration, arterial hypotension, a significant decrease in the formation of macroergs in tissues, depletion of muscle glycogen, impaired microcirculation and a decrease in oxygen utilization by tissues are the main reasons for the increase in general weakness and fatigue, which are among the earliest manifestations of the disease. Since the disease usually develops slowly, during a long initial period unmotivated weakness and fatigue are often the only complaints of patients. At the debut stage, these symptoms appear only towards the end of the day, but later they become permanent, acquiring the character of adynamia and asthenia in severe cases.

These symptoms are characteristic of all cases of primary CAI, and in untreated patients, asthenia can be so pronounced that it is observed even when the patient is in bed. Rest does not bring relief and the patient is unable to take active action. Other manifestations are also noted:

– cardiac weakness, when heart sounds are muffled, and the pulse on the radial artery may be small and thread-like;

– darkening of the eyes, attacks of dizziness and fainting.

In some cases, intravenous administration of refined salt and liquid stops an attack of asthenia. This confirms that an important cause of weakness in Addison's disease is impaired electrolyte metabolism and associated dehydration. However, this symptom is also caused by disturbances in protein and carbohydrate metabolism. For this reason, the best effect in the fight against asthenia is achieved by the combined use of mineralocorticoids and GCs. The severity of asthenia reflects the severity of the disease; during addisonian crises it reaches its maximum degree. In mild forms of the disease, muscle weakness is mild, and the patient may remain able to work. In addition to severe muscle weakness, patients with Addison's disease are characterized by various neuropsychic disorders: rapid mental fatigue, lethargy, irritability, isolation.

In the objective status of patients, the decrease in body weight, often significant, usually correlates with the severity of gastrointestinal disorders, deserves special attention. Weight loss – is a typical manifestation of primary CAI; The progression of the mass noted in the anamnesis can serve as a sign that excludes the assumption of this disease. Weight loss is associated with loss of appetite and gastrointestinal disorders, as well as gradually developing dehydration.

A clinical manifestation reflecting the degree of corticosteroid deficiency and disturbances in water-electrolyte metabolism is considered to be arterial hypotension – a cardinal sign of primary CAI. The magnitude of the increase in blood pressure (BP) depends on its level before the disease. In some cases, even with severe adrenal insufficiency, arterial hypotension may be absent. This is observed in patients with hypertension or symptomatic arterial hypotension. The direct dependence of BP levels on the degree of adrenal insufficiency is confirmed by its sharp decrease during Addisonian crisis, which is a formidable symptom. Hypotension, which is accompanied by dizziness, blurred vision, general weakness and tachycardia, – often occurs when the body position changes, especially when getting out of bed in the morning. Dizziness and fainting after quickly assuming a vertical position may be the first manifestations of the disease.

The pathogenesis of arterial hypotension in Addison's disease is based on an absolute deficiency of mineralocorticoids, leading to the development of hyponat-remia, hyperkalemia and ketosis. Dehydration with a decrease in circulating blood volume is a consequence of increased loss of sodium and water through the kidneys and gastrointestinal tract. Reducing the sodium content in the walls

of small vessels (arterioles) reduces the pressor effect of norepinephrine and other vasoactive substances, which leads to a decrease in peripheral resistance and blood pressure. A decrease in the volume of circulating blood leads to: an increase in intracellular dehydration, aggravation of arterial hypotension – to a collaptoid state; a decrease in cardiac output and glomerular filtration, which may be accompanied by anuria. The normalizing effect on BP of excessively administered refined salt obviously comes down to fluid retention in the body and an increase in the volume of circulating blood. It is noteworthy that adding salt to the diet in patients with hypocorticism never leads to hypertension. Some patients have an increased craving for refined salt.

Depletion of energy reserves and profound dystrophic changes in the myocardium associated with metabolic disorders lead to a decrease in the voltage of the electrocardiogram waves, especially the T wave, a decrease in the S-T interval, prolongation of the P-Q and Q-T intervals, and expansion of the QRS complex.

Pigmentation of the skin and mucous membranes, associated with the deposition of melanin, is an early symptom of the disease and can appear long before the appearance of other symptoms. Increased deposition of melanin is observed, first of all, on exposed parts of the body exposed to sunlight – on the face, neck, dorsum of the hands and feet, especially in the area of the interphalangeal joints. The back surfaces of the elbow joints, folds and folds of the skin, places of friction of clothing, burns and scars, palmar lines, halos of the nipples of the mammary glands, areas around the anus and external genitalia are also pigmented. As the disease progresses, pigmentation becomes diffuse, remaining more pronounced in the above areas. The skin acquires a bronze color, sometimes a dirty brown or golden hue, the color of an intense sun tan. A fairly specific, but not always pronounced sign is the presence of pigment spots on the mucous membranes of the lips, gums, cheeks, soft and hard palate. This sign has great diagnostic value, taking into account the national or racial pigmentation of the skin.

The degree of hyperpigmentation does not always reflect the severity of the disease, therefore cases of the disease with mildly expressed pigmentation or in the complete absence of this sign, which is extremely rare, cannot be regarded as a manifestation of a mild form of chronic adrenal insufficiency. Increased pigmentation of the skin and mucous membranes indicates an increase in the severity of the disease and is a prognostic sign of the development of Addisonian crisis. On the contrary, lightening of the skin and mucous membranes is observed with compensation of adrenal insufficiency, achieved by prescribing adequate replacement therapy. Several theories have been proposed to explain the mechanisms of pigmentation development in primary CAI, but currently this symptom is associated with hyperstimulation of melanocortin-1 receptors due to excess ACTH.

In some patients with primary CAI, areas of depigmentation (vitiligo) are found against the background of general hyperpigmentation, which confirms the autoimmune genesis of the disease. These spots do not have a specific localization, their sizes vary – from small and barely noticeable to large ones that clearly stand out against the general hyperpigmented background.

The appearance of symptoms of damage to the gastrointestinal tract

In Addison's disease, it always indicates significant destruction of the adrenal cortex. Lack of appetite is usually the first sign of the disease; as it progresses, patients with hypocorticism often find: hypoacid gastritis, spastic colitis, ulcerative lesions of the stomach and duodenum. The predominance of complaints of gastrointestinal disorders, for which patients are observed for a long time by a gastroenterologist, leads to a late diagnosis of chronic adrenal insufficiency.

Sometimes, in severe cases of the disease, abdominal pain can be significant and is accompanied by muscle tension in the anterior abdominal wall and symptoms of peritoneal irritation. This picture is often diagnosed as «abdominal catastrophe» – with unjustified surgical interventions. The pathogenesis of gastrointestinal disorders is explained by a decrease in the acidity of gastric juice, which is largely associated with a decrease in the content of sodium and chlorine ions in the body. Patients experience a decrease in the concentration of free hydrochloric acid in the gastric juice, and true achlorhydria is often observed. The role of achlorhydria in the development of gastrointestinal disorders is small, since the same symptoms are noted in patients with both normal and sharply reduced acidity. Administration of dilute hydrochloric acid to patients with achlorhydria does not eliminate anorexia, nausea and diarrhea.

The appearance of gastrointestinal symptoms indicates an impending Addisonian crisis, and vomiting and diarrhea arising from other causes contribute to the acceleration of the development of acute adrenal insufficiency. Associated with glucocorticoid deficiency, disturbances in the processes of gluconeogenesis and glucose absorption in the intestine, increased sensitivity to insulin can provoke hypoglycemia on an empty stomach or after eating a meal rich in carbohydrates.

Hypoglycemic conditions in patients with hypocorticism are often mild, accompanied by a feeling of hunger, sweating, and emotional disturbances, but in some cases hypoglycemic coma may develop. Hypoglycemia develops due to the fact that, under conditions of decreased cortisol secretion, gluconeogenesis is inhibited and glycogen reserves in the liver are depleted.

Against the background of a decrease in glomerular filtration and renal blood flow associated with a decrease in circulating blood mass and arterial hypertension, nocturia is often observed in patients with hypocorticism. The typical clinical picture of the disease develops gradually; against the background of its slow progression, sharp decompensation is possible, the provoking factors of which are infectious diseases, severe stress conditions, pregnancy, and childbirth. Therefore, primary CAI is often first diagnosed in patients in a state of Addisonian crisis.

In a small proportion of patients with late diagnosis of hypocorticism, calcification of the ear cartilage is detected, which is probably due to hypercalcemia.

A decrease in the secretion of adrenal androgens has little effect on the state of sexual functions in men if testicular function is preserved; in women, this may be associated with: decreased libido, as well as a decrease or disappearance of axillary and pubic hair. Amenorrhea can be associated with both weight loss and primary ovarian failure.

The most typical manifestations of hypocorticism syndrome include general weakness.

Based on the severity, CAI can be divided into three forms: mild, moderate and severe. For the assessment, both the severity of the main clinical manifestations of diseases (adynamia, hypotension, gastrointestinal disorders, etc.) and the treatment necessary for the patient's well-being and restoration of metabolic disorders are taken into account.

- In mild forms, patients feel satisfactorily without the use of hormone replacement therapy, limiting themselves only to taking ascorbic acid and following a diet – adding salt to food and limiting potassium.
- In case of moderate disease, the use of glucocorticoid drugs is necessary to normalize BP, increase body weight and restore metabolic disorders.
- For severe forms, especially if there is a history of Addisonian crises, the treatment complex necessarily includes regular intake of not only GCs, but also mineralocorticoids.

The erased form of primary CAI is characterized by the absence of noticeable weight loss, slight hypertension and mild severity of other clinical symptoms – muscle weakness, gastrointestinal disorders. An important diagnostic sign is the presence of pigmentation; to make a final diagnosis, a detailed clinical examination and assessment of hormonal parameters, including the results of functional tests, are necessary.

Diagnosis

The diagnostic search for primary CAI includes three stages – clinical, laboratory and etiological.

1. At the first stage, based on an assessment of complaints, anamnestic data and objective clinical signs, an assumption about the presence of a disease is formed.
2. At the stage of laboratory diagnostics, the presence of corticosteroid deficiency is confirmed/excluded.
3. Etiological diagnosis is aimed at identifying the cause of destruction of the adrenal cortex.

The main clinical manifestations include: general weakness, adynamia, skin hyperpigmentation, weight loss, arterial hypotension, gastrointestinal disorders, and attacks of hypoglycemia.

None of these symptoms, considered separately, has 100 % specificity for primary CAI – only their combination is diagnostically significant. The most informative – is the combination of asthenia and adynamia with weight loss, hypotension and melasma. As you can see, diagnosing typical cases of the disease does not present any great difficulties for a clinician-endocrinologist, and hormonal examination can be limited to determining the level of cortisol in the blood and its daily excretion in the urine. Anamnestic data confirming the diagnosis include: the gradual development of the clinical picture and the frequency of periods of deterioration in the well-being of patients – usually against the background of stressful conditions, in the spring and autumn seasons.

The results of general clinical and biochemical blood tests are of limited value in the diagnosis of primary CAI. Patients are found to have **nonspecific laboratory parameters** – electrolyte disturbances: hyperkalemia; hyponatremia; normochromic or hypochromic anemia; moderate leukopenia; relative lymphocytosis and eosinophilia. With a concomitant inflammatory process, an increase in erythrocyte sedimentation rate is possible.

Primary CAI is characterized by an increase in plasma renin activity, which serves as one of its differential diagnostic features in comparison to secondary forms of the disease. In a biochemical blood test, the levels of nitrogen, urea and creatinine are often elevated, which is caused by hypovolemia, a decrease in the glomerular filtration rate and renal blood flow. Fasting blood sugar levels are often reduced, and the glycemic curve after a glucose load is torpid in nature with a hypoglycemic phase.

Some patients experience hypercalciuria and hypercalcemia of unknown origin. The detection of hypocalcemia in patients with hypocorticism should alert us to the presence of hypoparathyroidism occurring as part of APS.

The first stage of hormonal studies has limited diagnostic value and includes: determination of basal levels of cortisol in the blood and daily excretion of free cortisol in the urine. With a detailed clinical picture of primary hypocorticism, a significant decrease in the daily excretion of free cortisol in the urine makes it possible to confirm the diagnosis and begin treatment. With partial damage to the adrenal cortex with mild manifestations of hypocorticism, these indicators may remain normal.

The basal blood ACTH level is not an indicator that confirms (or excludes) the diagnosis of primary CAI; it is determined to establish the genesis of hypocorticism – primarily adrenal or hypothalamic-pituitary.

With a blurred clinical picture, an atypical course, especially when the results of laboratory parameters determined under basal conditions have borderline values or do not exceed normal limits, it is difficult to diagnose CAI. In such situations, the diagnostic value of functional tests increases, among which stimulation tests with pharmacological ACTH preparations are considered the most reliable.

Short-term intravenous corticotropin test 250 mcg (25 IU) per 5 ml saline or 1-24-ACTH test (first 24 amino acids 39 amino acid molecule ACTH) – with a study of plasma cortisol levels 30 and 60 minutes after administration of the drug – allows you to assess the available reserves of the adrenal cortex. Carrying out a test with 1-24-ACTH is advisable in a situation where:

– the doctor does not have experience working with patients suffering from primary CAI;

– the patient does not have at least one of these symptoms: severe melasma, weight loss, arterial hypotension and dyspepsia.

With normal function of the adrenal cortex, under the influence of administered ACTH, the blood cortisol level increases 2–3 times. When assessing the results of an ACTH test, the increase in blood cortisol relative to its initial level is taken into account. The relative increase in cortisol is inversely proportional to its basal level, so in the morning, when the levels of ACTH and cortisol in the blood are maximum, its value may be small. In other words, with such an assessment, the results of the ACTH test may be biased. The assessment of the peak cortisol level after the administration of ACTH is considered more reliable, when an increase in this indicator – to 500–550 nmol/l and above – reliably excludes primary CAI.

Short-acting drugs ACTH1-24 are not available on the Ukrainian pharmaceutical market. In clinical practice, modifications of the test are used – with the use of a prolonged synthetic analogue of ACTH - Tetracosactide (Synacthen depot).

The diagnosis of complete (absolute) primary CAI is confirmed when the content of free cortisol in daily urine remains equally low on all days of the test – as before the administration of the drug. With relative adrenal insufficiency, the initial content of free cortisol in the urine may be normal or reduced. On the first day of stimulation, it increases similar to the normal increase, but on the third day it decreases to subnormal values. A similar result of a long-term test with Synacthen depot confirms the absence/reduction of potential reserves of the adrenal cortex when available reserves are preserved. In case of secondary adrenal insufficiency, on the first day of administration of Synacthen depot there may be no increase in cortisol in the urine, but on days 3 and 5 the reaction to stimulation reaches normal values.

In patients at risk of developing secondary CAI, when ACTH is not available, the functional state of the hypothalamic-pituitary-adrenal system is examined using an insulin tolerance test. Insulin is administered intravenously at a dose of 0,1–0,15 mg/per 1 kg of body weight, the level of cortisol in the blood is examined before insulin administration, and then after 30 and 60 minutes. The most important indicator in this test is the peak level of blood cortisol (see section «Hypocorticism of central origin»).

After diagnosing primary CAI, an **etiological diagnosis of the disease** should follow, which involves, first of all, confirmation/exclusion of adrenal tuberculosis.

The tuberculous genesis of CAI is confirmed by detecting calcifications in the adrenal glands and identifying foci of tuberculosis in other organs using chest x-ray. At the same time, the diagnostic value of chest x-ray in the diagnosis of organ tuberculosis is not absolute, since primary CAI of tuberculous origin may not have visible pulmonary damage. On the other hand, the detection of old calcification or primary tuberculosis complex in the lungs cannot reliably exclude autoimmune damage to the adrenal cortex or another genesis of its insufficiency.

This position is confirmed by cases of primary CAI, combined with autoimmune thyroiditis, which are observed in patients with the presence of old tuberculous lesions. Cases of active tuberculosis in the lungs have been described in patients with CAI caused by atrophy and metastatic lesions of the adrenal glands. Since the tuberculous process in the adrenal glands is often combined with damage to the genitourinary system, instrumental studies of the pelvic organs are required. In some cases, damage to the adrenal glands by Mycobacterium tuberculosis is confirmed by tuberculin tests, polymerase chain reaction of urine and sputum cultures.

Among imaging methods, computed tomography (CT scans) of the retroperitoneal space has the greatest diagnostic significance. In autoimmune Addison's disease, bilateral adrenal atrophy of varying severity is detected; in the majority of patients with newly diagnosed hypocorticism of tuberculous etiology, the size of the adrenal glands is increased. Over time, in the later stages of the disease, the size of the adrenal glands affected by tuberculosis decreases due to atrophic changes. They often contain areas of necrosis and calcification.

Enlargement of the adrenal glands detected on CT scans is observed not only with tuberculosis, but also with fungal and parasitic lesions of the adrenal glands, tumor or metastatic lesions. In difficult cases of etiological diagnosis of CAI, the method of fine-needle aspiration biopsy of the adrenal glands is used, which is carried out under ultrasound or CT scans control. The indication for the study is a significant enlargement of the adrenal glands or the need for differential diagnosis of tuberculosis lesions with another pathology: tumor metastases, fungal infection.

In the absence of data on the tuberculosis process, idiopathic (autoimmune) Addison's disease is accepted as a presumptive diagnosis. A strong argument in its favor is the presence of concomitant autoimmune endocrinopathies in the patient, in particular APS. Antibodies to the enzymes of adrenal steroidogenesis: 21-hydroxylase (P 450 c 21), 17 α-hydroxylase (P 450 c 17) and side chain uncoupling enzyme (P 450 scc) – serve as specific immunological markers of autoimmune destruction of the adrenal cortex. The most accessible test today is the determination of antibodies to P 450 c 21; detection of the latter eliminates the need for other laboratory and instrumental studies for the etiological diagnosis of primary CAI and allows us to exclude other endocrine diseases of autoimmune origin.

In clinical practice, situations often arise when, by the time the final diagnosis of «primary CAI» was made, the patient had already been prescribed corticosteroid replacement therapy. In this case, the patient must be switched to dexamethasone for several days (0,25–0,5 mg/day) to exclude cross-reaction of exogenous corticosteroid with endogenous cortisol. An ACTH test is performed no earlier than 24 hours after discontinuation of dexamethasone and is interpreted in accordance with generally accepted recommendations.

Differential diagnosis

To confirm the diagnosis of primary CAI, it is necessary to exclude other diseases that occur with a similar symptom complex: increased muscle weakness, weight loss, hypotension, skin hyperpigmentation and gastrointestinal disorders.

With neurocirculatory dystonia of the hypotensive type, muscle weakness is usually intermittent, intensifies under the influence of psycho-emotional factors, and is more pronounced in the morning.

General weakness and anorexia are observed in patients with neurasthenia, and arterial hypotension is often noted. The lability of symptoms, the absence of pigmentation, orthostatic hypotension, hypoglycemia, and the results of functional studies of the adrenal cortex make it possible to differentiate this disease from primary CAI.

The presence of arterial hypotension with low body weight requires the exclusion of essential hypertension. Progressive weight loss is often observed in chronic diseases of the gastrointestinal tract, cancer pathology, various intoxications, and anorexia nervosa. In these diseases, general weakness rarely takes on the character of adynamia; patients are not characterized by severe arterial hypotension. In diagnosis, a carefully collected anamnesis and the results of additional studies are important.

Skin hyperpigmentation, characteristic of thyrotoxicosis, is usually evenly and moderately expressed, mainly localized around the eyes. Unlike Addison's disease, weight loss is accompanied by normal or increased appetite, persistent tachycardia, systolic hypertension, sonorous heart sounds, and a normal glycemic curve. Some patients with severe thyrotoxicosis may develop CAI, accompanied by arterial hypotension; to clarify the functional state of the adrenal cortex, additional examination is required.

With hemachromatosis, in contrast to Addison's disease, pigmentation is accompanied by an enlarged liver (liver cirrhosis), fasting hyperglycemia or diabetic glycemic curve, increased iron content in the blood serum; the pigment hemosiderin is found in the skin, liver and bone marrow.

In patients with arterial hypotension, Addison's disease can be imitated by sunburn and a certain race of the patient. In this case, you should pay attention to the absence of pigmentation in closed areas of the body, palmar grooves, mucous membranes, and scar sites. It is necessary to take into account that

under the influence of excess solar radiation, the transition of latent adrenal insufficiency into a clinically pronounced form of the disease is possible.

Scleroderma is characterized by dense or thickened skin pigmentation, which is not characteristic of Addison's disease.

Porphyria, which is accompanied by generalized brown pigmentation of the skin, is characterized by the presence of large amounts of uroporphyrin in the blood plasma, urine and feces.

In pellagra, pigmented areas of skin are located on the extremities in the form of «socks» and «gloves», as well as on the neck. These features, as well as diarrhea and dementia accompanying pellagra, are not typical for Addison's disease.

Changes in skin color, inherent in primary CAI, are observed in patients with chronic poisoning with salts of heavy metals – arsenic, zinc, lead, mercury, silver. A specific medical history, as well as the absence of other signs of hypocorticism, can exclude the diagnosis of Addison's disease.

Primary CAI, as an independent disease, must be differentiated from secondary forms and genetic syndromes that are accompanied by hypocorticism.

Treatment tactics

General treatment principles

When prescribing therapeutic measures for patients with CAI, the etiology of the disease should be taken into account. Timely adequate therapy for tuberculosis, sepsis, fungal and other diseases that are associated with the development of hypocorticism protects the adrenal cortex from further destruction, and the remaining tissue hypertrophies compensatory.

Treatment is aimed at eliminating clinical manifestations, normalizing impaired metabolic processes and restoring the ability of patients to work. In addition, therapeutic measures prescribed to patients with CAI should prevent the development of Addisonian crisis.

The choice of treatment method outside of a crisis is determined by the severity of adrenal insufficiency. With a mild form of the disease, patients feel quite satisfactory without the use of hormonal drugs, since their condition is fully compensated by diet.

The total calorie content of food of patients with CAI is 20–25 % higher than usual for a given age, gender and profession, with a sufficient amount of protein (1,5–2 g/kg), carbohydrates and fats. Of the fats, butter is preferable, containing vitamins and easily utilized. The diet includes a sufficient amount of carbohydrates, including easily digestible ones. To avoid the development of a hypoglycemic reaction, it is recommended to consume carbohydrates in fractions. Additionally, patients are prescribed refined salt up to 10–15 g per day; limit the consumption of foods rich in potassium salts – prunes, apricots, raisins, chocolate, cocoa, baked potatoes. The diet includes vegetables and fruits, juices.

In severe forms of adrenal insufficiency, it is necessary to compensate for the deficiency of gluco- and mineralocorticoids, and therefore it is preferable to

use drugs that have both activities – hydrocortisone and cortisone. Provided that increased amounts of sodium chloride are included in the diet, these drugs are sufficient and additional mineralocorticoids are not required. In practice, most patients need not only gluco-, but also mineralocorticoids. When using prednisolone and other drugs with glucocorticoid action, mineralocorticoids must be additionally prescribed. In this case, there is no need to add salt to food or limit potassium-rich foods – mineralocorticoids normalize water-electrolyte metabolism.

In patients with CAI, hormone replacement therapy is carried out for health reasons; for this reason, known contraindications are not taken into account. The administration of GCs should satisfy the physiological needs of the body and simulate the daily rhythm of their secretion. In this regard, about 2/3 of the total dose of the drug is recommended to be taken in the morning, and the remaining part – during the day or in the evening, depending on the frequency of administration.

Patients with an established diagnosis of CAI take corticosteroid drugs for life with individual dosage selection. It should be minimal, but sufficient to maintain the patient's normal well-being and compensate for metabolic disorders. Doses of corticosteroids are selected depending on the severity of the disease, and taking into account the patient's condition – rest, stress, intercurrent illnesses, etc.

Patients with CAI advised to transfer to light work with a normalized working day, excluding night shifts, business trips – and heavy physical activity. During the period of decompensation of hypocorticism, patients are unable to work. In severe cases of the disease, transfer to disability is indicated.

The mechanisms of action of corticosteroids

Corticosteroids act by binding to intracellular steroid receptors and regulate gene expression – at the transcriptional and posttranscriptional levels. The multifaceted influence of GCs on metabolism ensures the body's adaptation to stress.

- Being counter-insulin hormones, they contribute to the development of hyperglycemia.
- Enhance the lipolytic effect of catecholamines and growth hormone, reduce the consumption and use of glucose by adipose tissue.
- Have an effect on protein metabolism: anabolic – in the liver; catabolic – in muscles, adipose and lymphoid tissues, skin, bones.

They inhibit the growth and division of fibroblasts and the formation of collagen, thereby disrupting the reparative phase of inflammation.

In accordance with the classical principle of negative feedback operating in the hypothalamic-pituitary-adrenal cortex system, GCs are endowed with ACTH-suppressive activity. GCs have a high affinity not only for their own receptors, but also for aldosterone receptors. The kidney enzyme – 11β-hydroxysteroiddehydrogenase, present in the kidneys, converts cortisol into the less biologically active cortisone. Of the corticosteroids, only aldosterone and fludrocortisone are not inactivated, which determines their high mineralocorticoid potential.

The main function of mineralocorticoids is to retain sodium in the body and maintain physiological osmolarity of the internal environment. The main target organ for mineralocorticoids is the kidney, where they enhance active sodium reabsorption in the distal convoluted tubules and collecting ducts by stimulating the expression of the Na^+/K^+-ATPase gene. In addition, mineralocorticoids promote the excretion of potassium, hydrogen and ammonium ions by the kidneys. When two sodium ions are reabsorbed, one potassium ion is released.

Modern corticosteroids are well absorbed from the gastrointestinal tract; food has little effect on drug absorption, although the rate of the process slows down somewhat.

The biological activity of a hormone is determined by its ability to bind to transport proteins. So, more than 90 % of cortisol is bound to serum proteins: about 80 % of the hormone is with the specific cortisol-binding globulin transcortin, and 10 % is with albumin. In contrast, synthetic GCs – with the exception of prednisolone – bind predominantly to albumin (about 60%); about 40 % circulate freely. The binding capacity of albumin (capacity) changes little.

With albumin deficiency and treatment with high doses of GCs, the free, biologically active part of the hormone may increase, which contributes to the development of side effects. Medicines, for example, indomethacin, displace corticoids from binding to proteins and enhance the effect of glucocorticoid therapy. The affinity of corticosteroids for transport proteins determines the relative activity and duration of action of the drug. For example, the greater activity of dexamethasone compared to cortisol is explained by its lower binding to blood proteins.

Medications used for hormone replacement therapy

GCs used in modern clinical practice include: cortisone acetate, hydrocortisone and their semisynthetic derivatives. The latter, in turn, are divided into non-fluorinated (prednisolone, methylprednisolone) and fluorinated (dexamethasone, triamcinolone).

The peculiarities of the use of injectable forms are determined both by the properties of the glucocorticoid itself and the ester associated with it. Thus, succinates, hemisuccinates and phosphates dissolve in water and, when administered parenterally, have a rapid but relatively short-term effect. In contrast, acetates and acetonides are finely crystalline suspensions and are insoluble in water. Their action develops slowly over several hours and is long-lasting. Water-soluble glucocorticoid esters, unlike fine-crystalline suspensions, can be used intravenously.

The structure of the molecules of cortisol (hydrocortisone), other commonly prescribed synthetic GCs and mineralocorticoids are presented in *Fig. 1*.

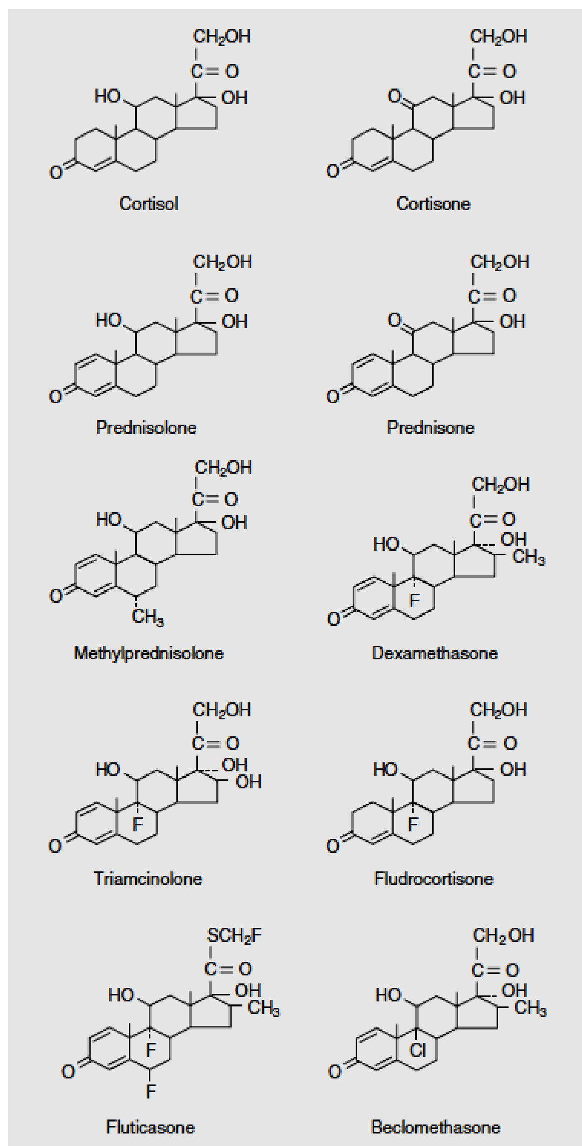

Fig. 1. Structure of corticosteroid drugs molecules (D. M. Williams)

When prescribing corticosteroid drugs for oral replacement therapy, it is necessary to take into account their glucocorticoid and mineralocorticoid activity, as well as dose equivalence and ACTH-suppressive effects, presented in *Table 2*.

Table 2

Comparative characteristics of corticosteroids

Medicines	Standard tablet form, equivalent in glucocorticoid activity, mg	Activity		
		Gluco-corticoid	Mineral-corticoid	ACTH-suppressing
Hydrocortisone	20	1	1	+
Cortisone	25	0,8	1	+
Prednisolone	5	4	0,5	+
Methylprednisolone	4	5	0,1	+
Dexamethasone	0,5	30	0,05	+++
Triamcinolone	4	5	0,05	++
Fludrocortisone	0,1	15	150	–

It must be taken into account that, depending on the duration of exposure, corticosteroids are divided into drugs:

- short action – duration of action less than 12 hours;
- average duration of action – duration of action 18–36 hours;
- long acting – duration of action 36–54 hours.

Differences in the duration of action of corticosteroids are associated with their pharmacokinetic characteristics: plasma half-life, half-life or tissue half-life, as presented in *Table 3*.

Table 3

Certain pharmacokinetic parameters of corticosteroids

Medicine	Duration of action	Half-life from plasma, hours	Half-life, hours
Hydrocortisone	short action	0,5–1,5	8–12
Cortisone-acetate	short action	0,7–2	8–12
Prednisolone	average duration of action	2–4	18–36
Methylprednisolone	average duration of action	2,4	18–36
Dexamethasone	average duration of action	3,5	18–36
Fludrocortisone	long acting	5	36–54

Hydrocortisone meets all the requirements for corticosteroids used for replacement therapy for CAI – it has both glucocorticoid and pronounced mineralocorticoid activity.

Cortisone is also endowed with glucocorticoid and mineralocorticoid activity, which is less pronounced compared to hydrocortisone. Unlike cortisol, cortisone has a keto group at position c-11 instead of a hydroxyl group. The transition of keto compounds to their active form occurs during metabolic hydroxylation in the liver, so severe damage to this organ is a contraindication for the administration of cortisone.

Prednisolone is less preferable for chronic replacement therapy in patients with CIU, since this drug has glucocorticoid and mineralocorticoid activity in a ratio of 300 : 1. The drug is used in combination with fludrocortisone.

Methylprednisolone has slightly greater glucocorticoid, but less mineralocorticoid activity compared to prednisolone (*Table 2*). The advantages of the drug include: weak stimulation of the psyche and appetite, good stomach tolerance. It is especially indicated for patients with unstable mental health, excess body weight, a tendency to gastric diseases, and muscle atrophy.

Dexamethasone, in comparison to prednisolone, has a better balance between glucocorticoid/anti-inflammatory and mineralocorticoid activity. To a greater extent than other corticosteroids, it suppresses the ACTH-function of the pituitary gland; this is a powerful psychostimulant, so long-term use of the drug is not recommended. If well tolerated by the stomach, it increases appetite and negatively affects calcium balance.

Triamcinolone has glucocorticoid activity comparable to prednisolone and lacks mineralocorticoid effect. The drug is characterized by slightly pronounced psychostimulation, increased appetite, and good stomach tolerance. However, its use is associated with the danger of myopathy and hirsutism.

The development of principles for glucocorticoid replacement therapy presents great difficulties, which is confirmed by the following provisions:

– secretion of GCs is normally circadian in nature;

– the main human glucocorticoid – cortisol and its synthetic analogues have a short half-life;

– there are no objective clinical and laboratory criteria for the adequacy of glucocorticoid replacement therapy;

– various glucocorticoid preparations can be used for replacement therapy of patients with CAI.

Tablet hydrocortisone is recognized as the most used glucocorticoid drug in the world for replacement therapy of patients with CAI; cortisone acetate is less commonly used. The disadvantage of synthetic drugs is their relatively narrow therapeutic range. It is hydrocortisone that is the drug of choice in children and adolescents, since growth retardation is possible during therapy with synthetic GCs. When using synthetic GCs, a higher incidence of osteopenia syndrome can be expected than when treated with hydrocortisone.

Certain difficulties are created by the relatively short period of action of hydrocortisone and cortisone acetate. When taking these drugs twice a day, complaints of weakness in the evening and early morning are quite typical, and therefore patients often prefer prednisolone with a longer action.

Treatment of patients with CAI with mineralocorticoids is widely used in clinical practice, which is determined by the following prerequisites:

– modern replacement therapy for hypocorticism with mineralocorticoids involves the use of only one drug – monotherapy with fludrocortisone (Cortineff);

– there is no significant daily dynamics of mineralocorticoid secretion, characteristic of GCs;

– physiological interactions between the adrenal cortex and the kidney are known and described in detail; potassium – sodium – renin – aldosterone – water balance – blood pressure.

Approximate corticosteroid replacement therapy regimens

The dose of prescribed drugs depends on the severity of the disease, the degree of compensation and the state in which the patient is – stress, rest. The decision on the dosage of the drug for replacement therapy is made based on data on body weight, well-being and BP levels.

Below is one of the approximate maintenance therapy regimens for patients with CAI.

Maintenance therapy
Replacement therapy
• Hydrocortisone 15–20 mg upon waking and 5–10 mg at the beginning of the day
• Monitoring clinical symptoms and morning plasma ACTH concentrations
Mineralocorticoid replacement therapy
• Fludrocortisone 0,1 (0,05–0,2) mg orally
• Free salt intake
• Monitoring BP while lying and standing, as well as pulse, edema, assessment of serum potassium concentration and plasma renin activity
• Patient education, including information about the disease: how to manage minor and serious diseases and how to administer intramuscular steroids
• Issuing a medical warning bracelet/chain, emergency medical information card to the patient

The following are recommended glucocorticoid replacement therapy regimens:

Using short-acting drugs:

– two-time regimen: hydrocortisone – 20 mg in the morning and 10 mg in the afternoon or cortisone acetate 25 mg and 12,5 mg, respectively;

– three times a day regimen: hydrocortisone – 15–20 mg in the morning, 5–10 mg in the afternoon and 5 mg in the evening or cortisone acetate 25 mg, 12,5 mg and 6,25 mg, respectively.

Using drugs of medium duration of action:

– prednisolone – 5 mg in the morning and 2,5 mg in the afternoon.

Using long-acting drugs:

– dexamethasone – 0,5 mg per day once late in the evening or in the morning.

Various combinations of these glucocorticoid drugs are possible. A mandatory component of any replacement therapy regimen is fludrocortisone at a dose of 0,05–0,1 mg (maximum dose 0,2 mg).

Thus, in the absence of pronounced stress loads, the usual maintenance daily doses of glucocorticoid drugs prescribed to adults along with 0,05–0,1 mg of fludrocortisone on average are: 20–30 mg of hydrocortisone, 25–37,5 mg of cortisone acetate, 5–7,5 mg prednisolone. The given replacement therapy regimens indicate the average, most commonly used doses of drugs.

Both the time of administration and the dose of GCs and fludrocortisone are selected individually. The following sequence of corticosteroid dose selection can be used:

– initially, the patient's condition normalizes due to hydrocortisone injections;

– then tableted hydrocortisone is prescribed at a dose of 30 mg/day or prednisolone at a dose of 10 mg/day (in 2 doses) in combination with fludrocortisone at a dose of 0,1 mg per day.

– then select the dose of fludrocortisone, focusing on plasma potassium levels and plasma renin activity levels in the morning.

– the next stage is a slow (in increments of 1 time per week) reduction in the dose of hydrocortisone

– at 5 mg or prednisolone at 2,5 mg until mild symptoms of hypocorticism appear, for example, evening weakness.

– after this, the dose of hydrocortisone or prednisolone is again slightly increased.

In case of severe decompensation of CAI, it is advisable to transfer patients to intramuscular injections of hydrocortisone – at least 3–4 injections per day at a dose of 75–100 mg – followed by a gradual reduction in the dose and transfer to oral administration of the drug.

Conditions required for carrying out corticosteroid replacement therapy

One of the most important conditions for the prevention of Addisonian crisis is education for patients suffering from CAI. It is necessary to inform everyone that the development of acute adrenal insufficiency can be triggered by any stress, febrile illness, injury, or surgery. Patients should clearly understand what symptoms accompany decompensation of the CAI, when the need for GCs increases significantly. Patients with CAI should be provided with hydrocortisone or synthetic GCs for injection, and syringes for their administration.

Preventing the development of Addisonian crisis involves increasing the dose of GCs in situations where the need for these drugs increases, as presented in the following recommendations:

Treatment of mild febrile illnesses or stress
• Increase the dose of GCs by 2–3 times over several days of illness; do not change the dose of mineralocorticoids.
• Consult a doctor if the disease worsens or persists for more than 3 days or if vomiting occurs.
• For outpatient dental interventions under local anesthesia, in the absence of complications, no additional medications are required. In outpatient dental care, general dental care should not be used, incl. internal anesthesia.
Emergency treatment for severe stress and trauma
• 4 mg of dexamethasone is administered intramuscularly
• See a doctor as soon as possible

Scope of use of steroids for diseases or surgery in a hospital
• For moderate diseases, 50 mg of hydrocortisone is prescribed twice a day orally or intravenously. Consecutive rapid reduction to a maintenance dose after the patient has recovered.
• For severe illnesses, 100 mg of hydrocortisone is prescribed intravenously every 8 hours. Consistently reduce the dose to maintenance (half the dose) every day. Adjust the dose of the drug in accordance with the course of the disease.
• For minor operations under local anesthesia and for most x-ray examinations, there is no need for additional medications.
• For interventions that cause a moderate stress response – such as irrigoscopy, endoscopy or arteriography – hydrocortisone is prescribed as a single dose of 100 mg intravenously immediately before the procedure.
• For large surgical interventions, hydrocortisone is prescribed 100 mg intravenously immediately before the administration of anesthetics and continue every 8 hours for the first 24 hours. Quickly reduce the dose by half per day to a maintenance level.

With the development of CAI in patients with hypertension, diabetes mellitus and thyrotoxicosis, the condition of the patients is often less severe than before this disease. However, when CAI is combined with hypertension or symptomatic arterial hypertension, it is advisable to prescribe corticosteroids with minimal mineralocorticoid effect. In patients with Addison's disease and diabetes mellitus, it is preferable to prescribe mineralocorticoids, which have virtually no effect on carbohydrate metabolism. Treatment of patients with CAI combined with thyrotoxicosis does not require adjustments.

For patients with hypothyroidism in combination with CAI, it is advisable to prescribe thyroid drugs only after compensation of hypocorticism is achieved with adequate doses of GCs and mineralocorticoids. Prescribing thyroid hormones to such patients without sufficient administration of corticosteroid drugs can cause a deterioration in the condition and provoke the development of Addisonian crisis.

In the treatment of CAI in patients suffering from gastric and/or duodenal ulcers, preference is given to mineralocorticoids. If the therapeutic effect is insufficient, additional prescription of GCs, starting with small doses, is carried out under the guise of antacid drugs – with the simultaneous administration of anabolic steroids. In cases of severe ulcerative lesions, patients are transferred to parenteral administration of GCs in combination with misoprostol drugs. Synthetic analogues of prostaglandin E 1 have a cytoprotective effect and increase the resistance of the gastrointestinal mucosa to harmful factors.

Since corticosteroids used in the treatment of patients with CAI interact with other drugs, it is necessary to take into account:

– antacids reduce the absorption of glucocorticosteroids when taken orally;

– phenytoin, barbiturates, rifampicin, diphenin, carbamazepine, diphenhydramine – increase the rate of biotransformation of corticosteroids by increasing the corresponding liver enzyme systems; isoniazid and erythromycin, on the contrary, slow down biotransformation;

– estrogens stimulate the production of transcortin in the liver, and therefore reduce the clearance of corticosteroids;

– diuretics and amphotericin β, when taken together with corticosteroids, increase the risk of developing hypokalemia.

If the dose of the corticosteroid used is large, and compensation for CAI does not occur, investigate the possible causes of this condition, check the expiration date of the drug, conduct an examination to exclude chronic infection and other concomitant diseases. The adequacy of replacement therapy with gluco- and mineralocorticoids will be assessed by targeted collection of anamnestic data from patients – to determine the general condition, assess physical activity, appetite and other clinical parameters. The dynamics of objective clinical indicators during treatment are also taken into account: BP levels, body weight, muscle strength, hyperpigmentation, electrocardiogram indicators, blood glucose and electrolytes.

The criterion for compensation of glucocorticoid deficiency is the normalization of ACTH concentration in the blood, and the criterion for mineralocorticoid deficiency is the normalization of plasma renin. Assessing indicators such as the level of blood cortisol and the content of free cortisol in daily urine – to assess the adequacy of replacement therapy – in patients with hypocorticism is not informative. The adequacy of treatment for patients with CAI is assessed separately by the mineralocorticoid and glucocorticoid components.

According to the mineralocorticoid component:

- normal plasma potassium and sodium levels;
- normal or moderately increased level of plasma renin activity;
- normal BP;
- absence of swelling, fluid retention – signs of drug overdose;

According to the glucocorticoid component:

- clinical presentation; reliable objective/laboratory criteria are not available;
- minimally expressed complaints of weakness and low performance;
- absence of pronounced hyperpigmentation of the skin and gradual regression of pigmentation;
- maintaining normal body weight, no complaints of constant hunger and signs of overdose: obesity, Cushingoid, osteopenia;
- absence of hypoglycemic episodes, normal BP.

The development of Cushing's syndrome during replacement therapy for CAI can be a consequence of an overdose of drugs with a glucocorticoid component; it directly depends on the dosage and duration of use. As a specific guideline for practice, it should be taken into account that for each GCs there is a threshold dose, prolonged excess of which leads to hypercortisolism. For hydrocortisone, this dose is 40 mg, for cortisone – 50 mg, for prednisolone – 10 mg, for methylprednisolone – 2–10 mg, for dexamethasone – 2 mg.

HYPOCORTICISM OF CENTRAL ORIGIN

Primary CAI should be differentiated from hypothalamic-pituitary insufficiency of the adrenal cortex. It is based on a violation of the production of corticotropin, which leads to a decrease in the secretion of steroids by the zona fasciculata and reticularis of the adrenal cortex. ACTH deficiency may be associated with primary damage to both the pituitary gland and the hypothalamus, which is accompanied by impaired synthesis of corticoliberin and a weakening of the regulatory influence of the hypothalamus on the functions of the pituitary gland.

ACTH-secreting cells are destroyed: with tumors of the sellar and parasellar region; pituitary ischemia; hemorrhages in the pituitary gland; «empty» sella syndrome; autoimmune lymphocytic hypophysitis; aneurysm of the internal carotid artery; thrombosis of the cavernous sinus; infectious diseases – tuberculosis, syphilis, malaria, meningitis; infiltrative lesions of the pituitary gland – hemochromatosis, histiocytosis X. Insufficiency of ACTH secretion can be iatrogenic – after irradiation of the pituitary gland or surgical intervention; associated with metabolic disorders, in particular chronic renal failure, syndrome of abnormal forms of ACTH and other genetic factors.

Often the cause of central hypocorticism is long-term use of GCs in various systemic diseases. Its severity ranges from functional disorders to morphological changes in the adrenal cortex, up to atrophy. Corticoliberin deficiency can be:

- a consequence of destruction of the pituitary stalk due to injury, compression by a tumor or aneurysm after neurosurgical surgery;
- the result of damage to the hypothalamus of a traumatic, tumor, inflammatory, toxic nature;
- associated with radiation.

Sometimes CAI develops in patients who have undergone unilateral adrenalectomy for corticosteroma. In this case, atrophy of the adrenal gland not affected by the tumor is caused by the suppression of corticoliberin and ACTH by excessively secreted GCs – via a feedback mechanism.

The symptoms of adrenal insufficiency of central origin are in many ways similar to the manifestations of primary CAI; its significant difference is the absence of hyperpigmentation. Clinically, symptoms caused by glucocorticoid deficiency dominate – general weakness, adynamia, hypoglycemia, weight loss, gastrointestinal disorders. Since the secretion of mineralocorticoids, to a lesser extent than the glucocorticoid function of the adrenal cortex, depends on the corticotropic function of the pituitary gland, central forms of CAI are not accompanied by hypoaldosteronism. As a result, water and electrolyte disturbances are not pronounced or absent.

In contrast to primary hypocorticism, with the pituitary genesis of the disease, symptoms of deficiency of other tropic hormones of the pituitary gland – somatotropic, thyrotropic and gonadotropic – are found.

Severe clinical manifestations of pituitary hormone deficiency (panhypopituitarism) occur when at least 90 % of its cells are destroyed. Symptoms can develop acutely, within several hours or days, which, in particular, is observed after neurosurgical intervention for a large pituitary tumor or after extensive hemorrhage into the pituitary gland. The disease can progress slowly, which is typical for hormonally inactive pituitary macroadenoma. In this case, from the moment of the appearance of nonspecific complaints – fatigue, weakness, decreased tolerance to physical activity – several years may pass until the diagnosis is established.

The clinical manifestations of hypopituitarism are varied and depend on the degree of deficiency of a particular pituitary hormone. The most typical symptoms of growth hormone deficiency include: an increase in the proportion of adipose tissue and a decrease in muscle mass, a decrease in the intensity of the basal metabolic rate, thinning and dryness of the skin, a decrease in bone mineral density, a decrease in myocardial contractility, and an increase in cholesterol levels in the blood.

Manifestations of gonadotropic insufficiency in women include: menstrual irregularities (amenorrhea, oligo (opsomenorrhea), infertility, decreased libido, hair loss in the armpits and pubis, atrophic changes in the vaginal mucosa, hypoplasia of the uterus and mammary glands.

Symptoms of secondary hypogonadism (gonadotropic insufficiency) in men include: decreased or absent sexual desire, erectile dysfunction, lack of ejaculation, decreased facial and torso hair, thinning scalp hair, pale skin, decreased pigmentation and folding of the scrotum, testicular density, oligoazoospermia.

In both women and men, long-term deficiency of sex hormones is associated with the development of osteoporosis and lipid metabolism disorders.

A defect in prolactin synthesis leads to agalactia. Along with this, post-traumatic hypothalamic panhypopituitarism due to the loss of prolactin-inhibiting factor can be combined with hyperprolactinemia. An increase in the level of prolactin in the blood in combination with hypopituitarism is also observed in malignant prolactinomas.

The presence of drowsiness, lethargy, memory loss, dry and pale skin, bradycardia and other symptoms of hypothyroidism in patients are a manifestation of thyroid-stimulating insufficiency (secondary hypothyroidism).

The severity of the clinical manifestations of hypopituitarism and the nature of its course are largely determined by a decrease in adrenal function, which aggravates general weakness, adynamia, and hypotension; promotes the development of hypoglycemia; reduces resistance to stressful situations and intercurrent diseases. Hypocorticism causes severe dyspeptic disorders, abdominal pain associated with spasm of intestinal smooth muscles, and atrophic processes in the gastrointestinal mucosa.

Adrenal insufficiency occupies a special place in clinical practice as an intractable side effect of glucocorticoid therapy, which is of great importance in many areas of medicine. Mild forms of long-term glucocorticoid therapy withdrawal syndrome are manifested by myalgia, fatigue, emotional instability, headache,

insomnia, loss of appetite, and nausea. Under basal conditions, these symptoms may remain latent. But reducing the patient's response to stress increases the risk of injuries, infections, surgical interventions and other stresses that can cause severe cardiovascular failure with possible death.

Severe forms of hypocorticism are dangerous due to the development of a panmesenchymal reaction with a febrile state and generalization of inflammatory reactions, including serositis and pulmonary infiltrates. This is due to the fact that, with long-term treatment, the tissues become accustomed to high levels of corticoids; they react to withdrawal with an outbreak of inflammatory processes. In such situations, it is necessary to reintroduce corticosteroids followed by an attempt at very careful gradual withdrawal.

The development of hypocorticism is possible after adrenalectomy for corticosteroma. The disease in this case is predominantly transient in nature and can last from several months to a year. The formation of adrenal insufficiency is associated with long-term suppression of ACTH by high concentrations of cortisol, autonomously produced by the tumor.

Diagnostic measures for hypocorticism of central origin include: a carefully collected anamnesis, detection of signs of pituitary insufficiency during physical examination; additional studies aimed at both laboratory confirmation of insufficiency of ACTH and other pituitary hormones, and elucidation of the cause of the disease.

The following categories of patients are subject to screening:

– with hypothalamic-pituitary neoplasms;

– infiltrative diseases of the brain or pituitary gland;

– those who have undergone irradiation of the head;

– survivors of severe brain injury;

– who have undergone surgery for macroadenoma or other pituitary tumors;

– with a history of pituitary apoplexy;

– women with massive blood loss during childbirth and postpartum arterial hypotension.

Iatrogenic adrenal insufficiency should be suspected in the following cases:

A. In a patient receiving prednisolone at a dose of 15–30 mg/day for 3–4 weeks. In such patients, after discontinuation of glucocorticoid therapy, depression of the hypothalamic-pituitary-adrenal axis may persist for 8–12 months.

B. In a patient receiving prednisone at a dose of 12,5 mg/day for 4 weeks. In this case, suppression of the hypothalamic-pituitary-adrenal system can persist for 1–4 months.

C. In a patient with Cushing's syndrome – after removal of an adenoma or malignant neoplasm of the adrenal gland.

D. In a patient with decreased cortisol secretion in response to ACTH receiving GCs, regardless of the dose and duration of glucocorticoid therapy.

Stimulation tests performed to diagnose corticotropic hormone deficiency include: ACTH test, insulin-induced hypoglycemia test, metopyrone test. In

this case, the most important indicator is the peak concentration of cortisol detected during the test.

To avoid the development of acute adrenal insufficiency, an ACTH test should be combined with prednisolone, which does not affect the determination of fluorogenic cortisol. In case of long-term course of the disease, due to atrophy of the adrenal cortex, the results of stimulation tests correspond to those observed in primary CAI:

– The content of electrolytes in the blood, as well as aldosterone, is not impaired, ACTH is reduced.

– Neutrophilia, eosinophilia, lymphocytosis, and decreased gastric secretory function are noted.

– Blood glucose levels are low.

– The glycemic curve after a glucose load is flattened.

If growth hormone deficiency is suspected, its basal concentration in the blood and its dynamics are examined under test conditions with hypoglycemia, clonidine, glucagon, and somatoliberin. Somatotropic hormone deficiency is confirmed by a low blood concentration of insulin-like growth factor-1, but normal levels of insulin-like growth factor-1 do not exclude somatotropic deficiency.

A violation of the gonadotropic function of the pituitary gland is evidenced by a decrease in the content of sex hormones in the blood – testosterone in men and estradiol in women – against the background of reduced concentrations of follicle-stimulating hormone and luteinizing hormone.

The presence of secondary hypothyroidism is confirmed by a reduced level of free thyroxine (T4) in the blood with an increase in the level of thyroid-stimulating hormone (TSH).

Instrumental examination of patients with suspected hypocorticism of central origin includes: magnetic resonance imaging (MRI scans) of the brain – to exclude organic brain damage; osteodentometry – if the disease lasts more than 12 months.

Panhypopituitarism, one of the components of which is hypocorticism of central origin, should be differentiated from anorexia nervosa and a number of diseases accompanied by weight loss: enterocolitis, malignant neoplasms, tuberculosis.

Treatment of patients with secondary hypocorticism should be aimed at compensating for hormonal deficiency, according to possibilities – eliminating the cause of the disease. As with primary CAI, replacement therapy is usually carried out with oral GCs. Only in severe cases or when the patient cannot take medications by mouth, parenteral routes of administration are used. The decision to prescribe GCs to a patient with secondary hypocorticism should be made in the presence of appropriate clinical symptoms, as well as on the basis of a low initial blood cortisol level or a disturbance in its response to stimulation.

For most patients, under normal conditions, oral cortisone or hydrocortisone in appropriate doses of 25 and 20 mg is sufficient. Under stress conditions – acute illnesses with high fever, injuries, etc. – the dose of GCs is increased by 2–3 times, and as the patient recovers from the state of stress, it is gradually reduced.

It is more difficult to develop treatment tactics for patients with partial ACTH deficiency, when, without stress, there are no clinical symptoms of hypocorticism. With proper training, many of these patients can do without hormone replacement therapy under normal conditions and only need it in stressful situations. Prescribing mineralocorticoids to patients with secondary adrenal insufficiency is usually not required. Otherwise, the treatment tactics correspond to those in patients with primary hypocorticism – this applies to crisis conditions, management of patients during surgical interventions. As the duration of the disease increases, the need for GCs may increase. If the secretion of other tropic hormones is insufficient, appropriate replacement therapy is required.

With iatrogenic hypocorticism, when there are no atrophic changes in the adrenal cortex, it is possible to restore the functional activity of the hypothalamic-pituitary-adrenal system. First of all, it is necessary to transfer the patient to short-acting GCs – hydrocortisone, prednisone, since the interval between doses of short-acting drugs is sufficient to partially restore the function of the hypothalamic-pituitary-adrenal system.

At the initial stage, GCs are taken daily in the early morning hours, which most closely corresponds to the physiological biorhythm of endogenous cortisol secretion. Then gradually switch from a single daily dose of the drug to a single dose every other day. Two options for changing the treatment regimen have been proposed: a one-time transfer to taking GCs every other day with doubling the dose of the drug; carryover of 5 mg from the daily dose of prednisone to the next day. When the dose of prednisone on the «fasting» day drops to 5 mg, it continues to be reduced at a rate of 1 mg per day. To fully restore the functional activity of the hypothalamic-pituitary-adrenal system, in conditions of a gradual reduction in the dose of prednisone taken, several months (sometimes up to a year) are required with monthly determination of blood cortisol levels. For a more detailed assessment of the functional state of the adrenal cortex, a corticotropin test is performed. If a reduced response to the administration of the drug is determined, then, in case of severe concomitant diseases, exogenous GCs may again be required.

In order to prevent the development of adrenal insufficiency, another scheme has been proposed, which involves taking into account the dose of corticosteroid and the duration of treatment.

At the European Symposium on Glucocorticoid Therapy, a Consensus on the nomenclature of doses and regimens of drugs was adopted. According to the Consensus, daily doses of GCs (in prednisolone equivalent) of 7,5 mg and below are designated as low; $> 7{,}5$ mg ≤ 30 mg – as average; $> 30 \leq 100$ mg – as high; > 100 mg – very high.

In patients receiving high and very high doses of drugs for several weeks, the dose is reduced by 10 % at intervals of 4 days. If such doses of the drug have been used for several months, then the same (10 %) reduction is carried out at intervals of several weeks. When treated with average doses of GCs, their

dosage is reduced by 10 % every 2 weeks. In patients receiving medium, high and very high doses of the drug for a long time, when reducing the dosage, pause at 7,5 mg of prednisolone. Subsequently, the dose is reduced at intervals of 1 mg per month.

ADRENAL INSUFFICIENCY IN CHILDREN

Hypofunction of the adrenal cortex in children, which is relatively rare, can be congenital or acquired, caused by both primary adrenal pathology and ACTH or corticoliberin deficiency.

The etiological factors for the development of adrenal insufficiency in children are similar to those in adults, with genetically determined pathology playing a leading role. According to I.I. Annikova (1974), boys are more likely to suffer from this disease. Tuberculosis etiology of the disease was identified in 8,8 % of cases. The mothers of the examined patients often had complicated heredity and difficult childbirth.

In most cases, the disease develops gradually, hyperpigmentation may be mild; among the leading symptoms are: weight loss, loss of appetite, delayed sexual development, delayed skeletal maturation, and often stunted growth. Muscle strength appears to be significantly reduced. Children with Addison's disease are also characterized by severe asthenia, dehydration, arterial hypotension, periodic vomiting and diarrhea, and hypoglycemic conditions. Sick children experience fatigue, memory loss, sleep disturbances, and they become indifferent to their surroundings.

In young children, chronic adrenal insufficiency can occur as Jacksonian epilepsy or meningitis, which makes diagnosis much more difficult. With erased forms of hypocorticism, its symptoms may be mildly expressed. Addisonian crisis in children often simulates toxic dyspepsia and meningeal syndrome. As noted by G. S. Zefirova (1963), during the period of Addisonian crises, clonicotonic convulsions and meningeal symptoms can manifest themselves in the normal composition of the cerebrospinal fluid.

The severe form of adrenal insufficiency is usually easily diagnosed by clinical manifestations and laboratory tests. To make a diagnosis of a hereditary or congenital disease accompanied by hypocorticism, in some cases the primary role is played by the assessment of its specific clinical manifestations.

When symptoms are mild, making a diagnosis of Addison's disease is difficult. Particular care should be taken when making this diagnosis in newborns, taking into account the fact that «... the positive effect of GCs cannot in any way serve as confirmation of hypocorticism».

When examining a child with suspected adrenal insufficiency, much attention is paid to the medical history, in particular, to find out whether the patient has been treated with corticosteroids. Pay attention to family history and the presence of other autoimmune endocrine diseases, especially hypoparathyroidism. Of the

functional tests, tests with ACTH and metyrapone have the greatest diagnostic value, before which they are treated with corticosteroids and infusion therapy. Increased secretion of ACTH against the background of a disproportionately low concentration of cortisol in the blood indicates primary adrenal insufficiency or resistance of the adrenal cortex to ACTH.

In case of acute adrenal insufficiency, a fluid infusion is immediately started – a 5 % glucose solution in a 0,9 % NaCl solution (450 ml/m^2) is administered over 30–60 minutes, then 3 200 ml/m^2/day. For hypoglycemia, glucose is prescribed in large quantities. Until the patient's condition stabilizes, hydrocortisone 2–5 mg/kg or equivalent doses of other GCs is administered intravenously every 4 hours. For hyponatremia or hyperkalemia, higher doses of hydrocortisone can be administered – 5–10 mg/kg every 6 hours. Fludrocortisone can also be given orally.

When prescribing replacement therapy, doses of GCs are selected individually to eliminate the symptoms of hypocorticism and ensure normal growth of the child. It is necessary to simulate the normal rate of cortisol secretion of 7–12 mg/m^2/day. Excess GCs inhibit a child's growth.

Recommendations for dosage of corticosteroid drugs are given in *Table 4*. Drugs such as prednisone, methylprednisolone, and dexamethasone are not recommended for use in infants and young children because it is difficult to accurately determine dosages that do not interfere with normal growth and simultaneously relieve symptoms of adrenal insufficiency. The volume of GCs for oral administration should be approximately twice the dose for parenteral administration.

Table 4

Maintenance and equivalent doses of GCs and mineralocorticoids used to treat adrenal insufficiency in children

Steroid	Daily dose, mg/m^2	Glucocorticoid activity	Mineral-corticoid activity
Hydrocortisone	15–20	1	1
Cortisone	20–25	0,8	2,5
Prednisolone	4–5	4-5	0,05
Dexamethasone	0,5–0,75	25-30	0
9α-fludrocortisone	0,05–0,3	10-15	80-100

Mineralocorticoid replacement therapy is only necessary for patients with primary adrenal insufficiency. Doses of mineralocorticoid drugs do not depend on the age and weight of the child (average doses of fludrocortisone are 0,05-0,2 mg/day), since the secretion of aldosterone changes slightly throughout life (in adults, serum aldosterone levels are only 2 times higher than in infants).

Additions of refined salt in a dose are usually 2–4 g/day.

HYPOCORTICISM AND PREGNANCY

Taking into account the possibility of using modern high-tech diagnostic and treatment methods, chronic adrenal insufficiency is not considered a contraindication for pregnancy or an indication for its termination. However, patients during this period require careful individual monitoring and urgent measures if necessary.

The literature provides experimental and clinical evidence of some improvement in the course of Addison's disease during pregnancy, due to the properties of the placenta to produce ACTH, as well as steroid compounds with gluco- and mineralocorticoid properties. This provision explains the recommendations given in some endocrinology guidelines to reduce the dose of glucocorticoid replacement therapy after the first trimester of pregnancy.

Today, clinicians and researchers agree that during this period the possibility of acute adrenal insufficiency cannot be excluded; At the same time, the main threat to a pregnant woman is intercurrent diseases. The need to increase the dose of fludrocortisone during pregnancy is justified by the fact that the level of progesterone, an antagonist of mineralocorticoid receptors, increases significantly, and the loss of sodium and water through sweat increases, which is observed in the summer, especially in hot climates.

Modern clinical endocrinology guidelines indicate that glucocorticoid replacement therapy before 3 months of pregnancy are carried out in the same doses as before pregnancy, then the dose of drugs is increased.

The development of an adrenal insufficiency crisis can be prevented by carefully monitoring the pregnant woman’s condition and teaching her the technique of independent adequate replacement therapy. In this regard, the following recommendations deserve attention.

- Initially, the doses of gluco- and mineralocorticoids used before pregnancy are continued – 15–10–5 mg of hydrocortisone or 5 mg and 2,5 mg of prednisolone plus 0,1 mg of fludrocortisone during the day.
- In case of vomiting, toxicosis of pregnancy, etc. – the dose of GCs is increased by 3–8 times.
- In case of hypotension, the dose of mineralocorticoids is increased by 2–3 times, in case of hypertension it is decreased.

Childbirth stress and loss of fetoplacental steroid production after childbirth pose the greatest threat to Addisonian crisis – these conditions require increasing doses of steroid drugs. During childbirth, it is recommended to administer hormones in the same way as during planned operations. It is recommended to increase the dose of the glucocorticoid drug on the eve of childbirth – hydrocortisone 40 mg 3 times a day or prednisolone 10 mg 3 times a day. During childbirth and in the first days after it, an infusion of 100–200 mg of hydrocortisone or 50 mg of prednisolone in a solution of NaCl and glucose is prescribed; in case of surgery, the dose of the drug is doubled.

Nelson's syndrome

In some patients who have undergone bilateral adrenalectomy for severe Itsenko-Cushing's disease, corticotropinoma with high ACTH secretion is formed, which is accompanied by adrenal insufficiency. This symptom complex is designated as «Nelson's Syndrome», named after the author (D. Nelson), who, together with his colleagues, first gave its clinical description in 1958. In a 33-year-old woman who underwent bilateral adrenalectomy, not only the clinical manifestations of the disease are described, but also its pathological features, as well as possible complications.

Today, the main methods of treatment for patients with Cushing's disease are surgical adrenalectomy and radiation therapy in combination with the prescription of medications to suppress ACTH secretion in the pituitary gland and block steroidogenesis in the adrenal cortex. Sometimes they may not be effective, which is an indication for removal of the adrenal glands. In extremely severe forms of Itsenko-Cushing's disease, total adrenalectomy is the method of choice to save the lives of patients.

The development of Nelson's syndrome is observed in 10–80 % of patients who have undergone such an operation. Young age is considered one of the risk factors, since the medical literature provides indications that this syndrome is not found in patients older than 36–40 years.

Disabling the function of the adrenal cortex, as the cause of the development of Nelson's syndrome, creates conditions for the development of pronounced disorders of the pituitary gland, which are assessed ambiguously.

Some researchers believe that the progressive increase in ACTH production, characteristic of this category of patients, confirms the development of a hyperplastic process in the pituitary gland with the formation of corticotropinoma.

According to others, the main factor in stimulating the growth of pituitary adenoma in Nelson's syndrome is the disappearance of hypercortisolemia associated with adrenalectomy, while maintaining the feedback mechanism. It has been proven that pituitary tumor receptors lose their specificity; their functions are not autonomous and depend on hypothalamic or central regulation. The latter is confirmed by the fact that in response to nonspecific stimulants, for example, thyrotropin-releasing hormone and metoclopramide, hypersecretion of ACTH is observed in patients with Nelson's syndrome.

A somatic defect in glucocorticoid receptors, which play an important role in the genesis of corticotropinoma, is explained by a mutation in the gene for these receptors in patients with Nelson's syndrome.

The features of the symptom complex observed in Nelson's syndrome are largely due to the extra-adrenal effects of excess production of ACTH by the pituitary gland. These include, first of all, the effect of excess ACTH on melanocytes, which is manifested by hyperpigmentation of the skin and mucous membranes. This action of ACTH is explained by the presence in its molecule of amino acid

residues, the sequence of which is the same for the ACTH molecule and melanocyte-stimulating hormone.

The extra-adrenal effects of ACTH include its effect on the peripheral metabolism of corticosteroids. With an excess of this hormone in patients with Nelson's syndrome, the half-life decreases and the metabolism of gluco- and mineralocorticoids taken to compensate for adrenal insufficiency is accelerated, resulting in an increased need for these hormones.

The formation of testicular, paratesticular and paraovarian tumors in Nelson's syndrome is also directly related to the extra-adrenal action of ACTH, due to the long-term stimulating effect of this hormone on the steroid-secreting cells of the gonads. In terms of clinical manifestations and the nature of steroidogenesis, tumors of the testicles and ovaries in patients with Nelson's syndrome are similar to tumors of the gonads in patients with congenital dysfunction of the adrenal cortex, which also develop in conditions of prolonged excess ACTH.

In 90 % of patients with Nelson's syndrome, a chromophobe pituitary adenoma is found, which in its structure is almost no different from the tumors observed in Itsenko-Cushing's disease and not subjected to total adrenalectomy. In Nelson's syndrome, most corticotropins are benign.

Clinical manifestations of Nelson's syndrome include: chronic adrenal insufficiency, often with a labile course; progressive hyperpigmentation of the skin and mucous membranes; neurological ophthalmological symptoms. The lability of the course of chronic adrenal insufficiency and the increased need for hormones prescribed as part of replacement therapy are due to the accelerated metabolism of gluco- and mineralocorticoids and a decrease in their half-life, which is typical for excess ACTH.

Hyperpigmentation of the skin and mucous membranes, the severity of which correlates with the degree of increase in ACTH levels in the blood, is an early and stable sign of Nelson's syndrome. The effect of ACTH on melanocytes is explained by the presence in its molecule of amino acid residues, the sequence of which is common with the molecule of α-melanocyte-stimulating hormone. Very dark coloration of the skin of open parts of the body, its folds and places of friction with clothing, hyperpigmentation with a purple tint of the mucous membranes are observed at ACTH concentrations above 1000 pg/ml.

Neurological and ophthalmological symptoms are determined by the presence of corticotropin, the size of the tumor, the nature and direction of its growth. With antesellar spread of the tumor, disturbances of smell and psyche are noted, with parasellar growth – symptoms of damage to the III–IV pairs of cranial nerves. The appearance of cerebral symptoms is associated with the suprasellar growth of corticotropinoma, germination or compression of the region of the third ventricle. Chiasmatic syndrome can manifest itself as bitemporal hemianopia, primary atrophy of the optic nerves of varying severity. The changes result in: decreased visual acuity, loss of lateral visual fields; blindness may develop in one or both eyes.

The psychoneurological status of patients with Nelson's syndrome is characterized by asthenophobic and asthenodepressive manifestations, neurotic syndrome, emotional instability, anxiety, and suspiciousness.

Spontaneous hemorrhages into the pituitary tumor, observed in rare cases of Nelson's syndrome, are accompanied by severe headaches, extensive neurological symptoms and signs of partial or total hypopituitarism.

Diagnosis of Nelson's syndrome is based on an assessment of clinical data and the results of determining the concentration of ACTH in the blood, confirmed by the detection of micro- or macroadenoma of the pituitary gland. Corticotropinoma that developed after total adrenalectomy is characterized by an increase in the level of ACTH in the blood of more than 200 pg/ml and a non-circadian rhythm in the production of this hormone. With the rapid growth of infiltrative adenomas, the ACTH level can reach 3 000 pg/ml.

In the diagnosis of Nelson's syndrome and its complications, an ophthalmological examination and assessment of the neurological status, confirmation of the presence of micro- or macroadenoma of the pituitary gland – with determination of the direction of tumor growth – are of great importance. The frequency of detection of pituitary microadenomas, in confirmation of the diagnosis, is increasing as high-resolution methods of topical diagnosis are improved.

Today these are contrast-enhanced CT and MRI scans.

Surgery, radiation and medications are used to treat patients with Nelson's syndrome. When removing pituitary microadenomas, preference is given to microsurgical operations with a transsphenoidal approach. For pituitary macroadenomas with invasive para-, supra-, or infrasellar growth, craniotomy with transfrontal access is used; if it is impossible to completely remove the tumor, additional radiation therapy is performed.

Radiation therapy (external gamma therapy or proton beam irradiation) with microcorticotropin competes with the transsphenoidal ablation method.

Drug treatment of patients with Nelson's syndrome includes hormone replacement therapy for adrenal insufficiency (following the same principles as for Addison's disease), as well as the use of ACTH-lowering agents. Cyproheptadine, bromocriptine, sodium valproate (Convulex) have an inhibitory effect on ACTH. There are reports of a decrease in ACTH levels in the blood using the somatostatin analogue octreotide.

Symptomatic treatment of patients with this syndrome is aimed at correcting disorders associated with sexual dysfunction, osteoporosis, obesity, post-radiation encephalopathy and other disorders.

To prevent Nelson's syndrome, it is necessary to:

– careful follow-up of patients who have undergone bilateral adrenalectomy;

– radiation therapy – preference is given to proton irradiation of the pituitary gland if it was not performed during the treatment of Itsenko-Cushing's disease;

– adequate compensation of adrenal insufficiency.

GENETIC SYNDROMES ACCOMPANIED BY HYPOCORTICISM

Adrenoleukodystrophy (Addison-Schilder disease, Simmerling-Creutzfeld disease, atrophy of the adrenal cortex with diffuse cerebral sclerosis). The listed terms refer to a disease first described as brown Shilder's disease, which is characterized by damage to the nervous system – with leukodystrophy in combination with hypocorticism. The group of leukodystrophies unites hereditary neurodegenerative diseases associated with the disintegration of myelin fibers of the central and peripheral nervous system.

Adrenoleukodystrophy, as a combination of adrenal insufficiency with progressive neurological disorders, is caused by defects in the ABCD1 gene, located on chromosome Xq28 and encoding the ALD protein. This protein, presumably a transport protein, is responsible for the transfer of Very long chain fatty acids into cellular peroxisomes, where their β-oxidation subsequently occurs. Impaired β-oxidation of long-chain fatty acids (LCFAs) in peroxisomes leads to their accumulation together with cholesteryl esters in all tissues, which is accompanied by their damage. First of all, myelin fibers of the central nervous system, cells of the adrenal cortex and testicles (Leydig cells) are affected.

According to modern concepts, adrenoleukodystrophy is not a rare disease, and is the third most common cause of primary hypocorticism – after autoimmune and tuberculous damage to the adrenal glands. This provision has replaced the previously generally accepted point of view about adrenoleukodystrophy as an extremely rare disease. This was facilitated by the introduction into clinical practice of highly informative laboratory tests and, first of all, determination of the content of LCFAs in the blood.

Several clinical variants of adrenoleukodystrophy have been described, the symptoms of which vary from severe, manifest to asymptomatic; Moreover, in the same family, as a rule, different forms are found. The advanced clinical form of the disease is characteristic of male hemizygotes; in heterozygous mothers and sisters of probands, its clinical picture is blurred, the so-called lyonization phenomenon. Based on the type of inheritance, there are 2 forms of adrenoleukodystrophy:

– one of them develops in infants and is inherited autosomal recessively;

– the second is inherited recessively, linked to the X chromosome and is more typical for older children and adolescents.

The autosomal recessive nature of the disease is confirmed by its isolated cases, which manifest themselves in the neonatal period in siblings of both sexes.

Neonatal adrenoleukodystrophy is characterized by multiple craniofacial dysmorphies: dolichocephaly, protruding wide forehead, wide nasal bridge, epicanthus, strabismus, «Gothic» palate, low-set ears, inverted nostrils, congenital cataracts. From birth the following symptoms are observed: convulsive syndrome, slowdown in physical and psychomotor development; Melasma and other manifestations of adrenal insufficiency subsequently develop.

About half of the cases of adrenoleukodystrophy occur in the cerebral form, which manifests itself in childhood in the form of static paraparesis, generalized ataxia, visual impairment, speech and swallowing, epileptic seizures and dementia. Hypocorticism manifests itself in childhood; signs of damage to the central nervous system – a little later, occasionally – simultaneously. The disease is severe and leads to death in childhood or adolescence. With a milder course of the disease, patients live longer, in which case they develop hypogonadism. Autopsy reveals atrophy of all layers of the adrenal cortex, as well as demyelination and diffuse sclerosis of the brain.

Adrenomyeloneuropathy, which is more common after age 15, affects the white matter of the spinal cord and peripheral nerves. The disease is characterized by a slow progression of peripheral motor and sensory neuropathy, which ultimately leads to spastic paraparesis. Clinical manifestations of adrenal insufficiency, as a rule, precede the development of neurological symptoms.

A rare form of the disease has been described, including, in addition to adrenal insufficiency: myopathy, delayed physical and psychomotor development, constipation, fatty liver, megalocornea, bladder ectasia.

The diagnosis of adrenoleukodystrophy is based on clinical data, the results of genealogical analysis, and data from laboratory and instrumental studies. It must be taken into account that the younger the man is at the time of manifestation of primary CAI, the greater the likelihood that the latter is associated with adreno-leukodystrophy. In addition to hypocorticism, signs of primary hypogonadism are often found. Adrenal insufficiency in patients with adrenoleukodystrophy has more pronounced manifestations compared to hypocorticism of other origins, which is due to concomitant neurological pathology. The diagnosis of adrenoleukodystrophy is also suggested in patients with primary CAI, who have a family history of early death in children, relatives with neurological diseases and/or hypocorticism.

Hormonal disorders associated with hypocorticism in adrenoleukodystrophy are nonspecific and, with a detailed clinical picture, include indicators of deficiency of gluco- and mineralocorticoids, increased levels of ACTH in the blood.

Specific diagnosis of adrenoleukodystrophy is based on identifying elevated levels of tetracosanoic and hexacosanoic fatty acids in the blood serum, as well as increasing the ratio of the levels of these and docasonic fatty acids.

The diagnosis is confirmed by the results of MRI scans of the brain, which reveals an asymmetric lesion involving the corpus callosum and periventricular parietooccipital white matter. In this disease, MRI scans also reveals spinal cord atrophy without disruption of the blood-brain barrier.

Treatment of adrenal insufficiency associated with adrenoleukodystrophy consists of constant use of corticosteroids, which does not prevent the appearance and progression of neurological disorders. A diet with a restriction of foods containing long-chain saturated fatty acids is pathogenetically justified. In the early stages of cerebral dysfunction, a relatively effective treatment is bone

marrow transplantation, which will prevent further demyelination. A high genetic risk for male siblings, the severity of the disease and the ineffectiveness of its treatment are factors that argue in favor of prenatal gender diagnosis, with subsequent continuation of pregnancy only if the XX karyotype is determined.

AUTOIMMUNE POLYENDOCRINE (POLYGLANDULAR) SYNDROMES (APS)

Autoimmune polyendocrine (polyglandular) syndromes (APS) – these are diseases associated with primary damage to two or more peripheral endocrine glands by an autoimmune process, leading to; as a rule, to their insufficiency, and often combined with autoimmune pathology of non-endocrine organs.

Many hypotheses explain the development of autoimmune target organ damage. The most popular one assumes the absence of immunological tolerance to target organ proteins of specific clones of CD4+ T lymphocytes. Cells of such clones produce cytokines, leading to autoimmune inflammation and organ destruction.

According to statistical studies, there is a tendency towards a gradual transition of Addison's disease to the category of APS. So, if in the 30–50s. of the last century, primary CAI within the framework of APS occurred in 13% of cases, then by the 80–90s. this figure increased to 34 %.

Below are 2 types of syndromes in which Addison's disease is an obligatory component.

Autoimmune polyendocrine syndrome type 1 (APS-1)

APS-1 is also referred to as candidal polyendocrine syndrome, Whitaker syndrome; APECED (autoimmune polyendocrinopathy candidiasis ectodermal dystrophy), MEDAC (multiple endocrine deficiency autoimmune candidiasis).

This disease with an autosomal recessive mode of inheritance is traditionally rare, but its relatively high frequency is noted in the population of Iranian Jews (1 : 6 000–9 000), in the Finnish population (1 : 25 000) and among residents of Sardinia in northern Italy (1 : 14 000). The discovery in 1997 of the gene responsible for the development of APS-1 became a new milestone in the history of endocrinology and immunology – the monogenic nature of an autoimmune disease was established for the first time. The gene, called AIRE (autoimmune regulator), is located on the long arm of chromosome 21 (21q22.3). The AIRE gene is a transcription factor and is expressed in the thymus, lymph nodes, and spleen. This gene is believed to be responsible for the normal immune response, and its polymorphism is associated with autoimmune diseases.

The main clinical manifestations of APS-1 include, along with primary chronic adrenal insufficiency, chronic mucocutaneous candidiasis and chronic hypoparathyroidism. To diagnose this syndrome, the presence of two of the three indicated components is sufficient, although the presence of all three diseases is possible, which usually develop in a certain chronological order: first, chronic candidomycosis appears, then hypoparathyroidism, and only then Addison’s disease.

These components of APS-1 usually develop during the first decade of life. Subsequently, other (minor) clinical manifestations of the syndrome appear:

- endocrinopathies – hypergonadotropic hypogonadism, autoimmune thyroid diseases, type 1 diabetes mellitus, lymphocytic hypophysitis;
- autoimmune diseases of the gastrointestinal tract – chronic atrophic gastritis, pernicious anemia, celiac disease;
- liver diseases – autoimmune hepatitis and cholelithiasis;
- malabsorption;
- autoimmune skin diseases – vitiligo and alopecia areata;
- malignant neoplasms.

New symptoms of the disease can appear throughout life, the periods between their occurrence vary – from several months to several decades.

Rare clinical manifestations of APS-1 include: vasculitis, hemolytic anemia, rheumatoid arthritis, tubulointerstitial nephritis with the development of chronic renal failure, metaphyseal dysplasia.

Chronic mucocutaneous candidiasis most often develops in children aged about 2 years. In this case, damage to the oral mucosa, genitals, as well as skin, periungual ridges, and nails is observed; damage to the gastrointestinal tract and respiratory tract is less common. The reason for this pathology is the selective immunological deficiency of T cells against Candida albians, which is confirmed by the absence of a skin reaction to fungal and tuberculin antigens. Patients maintain normal β-cell response, which prevents the development of systemic candidiasis.

Chronic candidiasis in children is often the only manifestation of APS-1 for many years, which is the reason for a more thorough examination of the child – for the purpose of early diagnosis of adrenal insufficiency, the acute manifestation of which can be fatal.

An important link in the diagnosis of APS-1 is family history: consanguineous marriages, cases of endocrine diseases, early disability or death among close relatives. The assessment of clinical, laboratory and instrumental studies necessary for the diagnosis of APS-1 is based on principles developed for individual endocrinopathies – components of the syndrome.

Molecular genetic diagnostic methods, in particular the determination of AIRE gene mutations, serve as confirmation of the diagnosis of APS-1 established at the clinical stage. They provide the opportunity to diagnose this disease before the formation of a typical clinical picture, when there are only initial clinical manifestations, for example, chronic candidiasis.

The type of inheritance of the disease is determined using genealogical analysis. If there is a high genetic risk, HLA testing may be recommended. Detection of HLA, DR3, DR4 antigens and the DR3/DR4 haplotype greatly increases the risk of developing APS-1. If these antigens are detected, it is advisable to study circulating antibodies, the detection of which serves as an

indication for prescribing preventive therapy. All patients with APS-1 should be evaluated by a dermatologist, dentist, and other specialists as needed.

The treatment strategy for patients with APS-1, aggravated by hypocorticism, consists of replacement therapy taking into account the damage to individual endocrine glands and is aimed at compensating for clinical symptoms of various organs and systems (the approaches are the same as for isolated forms of endocrinopathies). The prescription of immunocorrective drugs is pathogenetically justified.

For the treatment of candidiasis of the skin and mucous membranes, the use of ketoconazole is undesirable, since this drug inhibits steroidogenesis in the adrenal cortex and can provoke the development of Addisonian crisis. Some features of replacement therapy when hypocorticism is combined with hypoparathyroidism are due to the fact that cortisol and vitamin D have opposite effects on intestinal calcium absorption. This means that in patients with adrenal insufficiency combined with hypoparathyroidism, the administration of large doses of GCs can provoke the development of severe hypocalcemia; with cortisol deficiency, there is an increased risk of vitamin D overdose.

Autoimmune polyendocrine syndrome type 2 (APS-2)

The autoimmune genesis of the disease is confirmed by the detection in the blood of patients of antibodies to the tissues of the endocrine glands involved in the pathogenetic process: the adrenal cortex, thyroid and pancreas. An autoimmune lesion is also supported by its close linkage with HLA system antigens (B8, DR3 and DR4).

The main components of APS-2 are Addison's disease, autoimmune thyroid diseases and type 1 diabetes. The most famous and common variant of the syndrome is a combination of primary adrenal insufficiency with autoimmune thyropathies (autoimmune thyroiditis or diffuse toxic goiter), known as Schmidt's syndrome. Less commonly diagnosed is the combination of primary adrenal insufficiency with type 1 diabetes – Carpenter's syndrome. There is also an opinion that Schmidt's syndrome should be considered: a combination of hypocorticism with insulin-dependent diabetes mellitus and autoimmune thyroiditis; the presence of at least two components from the specified triad of diseases.

APS-2 occurs with an incidence of 1,4–4,5 cases per 100 000 people and affects mainly adult women; peak incidence is 30 years. When examining the adrenal glands using CT or MRI scans, normal or reduced sizes of the glands are usually detected; only in patients with a long history of the disease, their atrophy is observed.

The clinical manifestations of Addison's disease in APS-2 and APS-1 are similar, with the exception of the age of its onset. APS-2 most often begins with diabetes, which in these cases is severe, with a tendency to ketoacidosis. If hypocorticism precedes the development of diabetes, the latter manifests itself in a milder form and is not complicated by ketoacidosis.

The functional state of the thyroid gland in APS-2 is more often described as hypo- or euthyroid, less often – it corresponds to thyrotoxicosis, which can be considered as different stages of the course of autoimmune thyroiditis.

Differential diagnostic features of APS-2 in comparison to APS-1 are presented in *Table 5*.

Table 5

Comparative characteristics of APS

APS type 1	APS type 2
Monogenic, autosomal recessive (Mendelian type of inheritance) disease with complete penetrance. In familial forms, it appears only in siblings. Peak manifestation at 12 years of age. Lack of association with HLA haplotypes, mutation in the AIRE gene on 21 q. 22.3 chromosome.	A disease with incomplete penetrance - hereditary predisposition (polygenic). In familial forms, it manifests itself in several generations. Peak manifestation at age 30. Association with HLA, B8, Dw3, Dr3, Dr4
Hypoparathyroidism, mucocutaneous candidiasis, chronic autoimmune hepatitis, malabsorption. Autoimmune thyropathies are relatively rare. Diabetes develops in 2–5 % of patients. The incidence ratio in men and women is 14 : 1. A characteristic difference between primary CAI within APS-1 is the relatively high frequency of detection of antibodies to P 450c17 and P 450 scc	These diseases are not observed. Autoimmune thyroiditis is an almost constant component. DM-1 is observed in 52 % of patients. The incidence ratio in men and women is 1 : 8. In case of primary CAI within the framework of APS-2, antibodies to P450 c17 and P 450 scc are relatively rarely detected, with a high frequency of antibodies to P450 c 21

Clinical and laboratory diagnosis of APS-2 is based on principles developed for the individual endocrinopathies that make up this syndrome. Severe APS-2 – with a full set of clinical manifestations of its constituent endocrinopathies – is quite rare; cases of incomplete forms of the disease are more numerous. The latter are considered to be conditions corresponding to the potential or subclinical stage of an autoimmune disease. For diagnosis, it is advisable to determine the content of TSH, free T3 and T4 in the blood, perform a glucose tolerance test and a test with corticotropin.

It is known that thyrotoxicosis as an independent disease can cause hyperpigmentation and other symptoms of hypocorticism associated with the intensification of cortisol metabolism and the induction of hepatic IIβ-hydroxy-steroiddehydrogenase, the enzyme responsible for the conversion of cortisol into cortisone. However, in this case, in contrast to true CAI, there is a normal release of cortisol under the conditions of an ACTH test. This fact must be taken into account if the presence of APS-2 is assumed when thyrotoxicosis is combined with hypocorticism.

The basic principles of treatment for patients with APS-2 are similar to those developed for certain forms of endocrine diseases. It should be taken into account that when adrenal insufficiency and hypothyroidism are combined, it is necessary, first of all, to prescribe replacement therapy with GCs and mineralo-corticoids. The reason for this is that taking thyroid drugs can aggravate uncom-pensated adrenal insufficiency and lead to the development of a crisis state.

CONGENITAL HYPOPLASIA OF THE ADRENAL CORTEX

The disease is based on a defect in the NROB1 gene, located on chromosome Xr21. The damaged gene encodes the DAX1 protein, which is involved in the differentiation of the adrenal cortex and the hypothalamic-pituitary-gonadal system. It manifests itself already in the first hours after birth – severe hypoglycemia, convulsive syndrome, collapse and vomiting. Over the next few days, diarrhea appears and exicosis develops. The mortality rate for this disease is very high.

Laboratory data – hyponatremia, hyperkalemia, hypocortisolemia, increased blood ACTH levels, etc. – confirm primary adrenal insufficiency.

The disease is inherited in an autosomal recessive manner or, more often, recessively, linked to the X chromosome. Clinically, the genetic variants are identical, differing in pathomorphological characteristics. The X-linked type of inheritance is characterized by tissue disorganization: with insufficient differentiation of cortical zones; cytomegaly and accumulation of eosinophils, resembling the structure of the fetal adrenal gland. The autosomal variant of the disease is characterized by more pronounced hypoplasia – in the absence of features typical of the embryonic adrenal cortex. Due to the predominance of the X-linked variant, boys are much more common among those affected.

As a rule, the disease manifests itself in the first month of life – symptoms of severe primary adrenal insufficiency. They differ: decreased appetite, frequent regurgitation, poor weight gain, hyperpigmentation, decreased tissue turgor. Hypoglycemia may develop – with convulsive syndrome, collapse and vomiting. Boys may have cryptorchidism at birth.

Laboratory examination reveals: hyponatremia, hyperkalemia, hypoglycemia, metabolic acidosis, decreased blood levels of cortisol, aldosterone and increased ACTH. The diagnosis can be verified using a molecular genetic study – analysis of the NROB1 gene.

Intensive replacement therapy with gluco- and mineralocorticoids is indicated. In the presence of hypogonadism, upon reaching puberty, boys are prescribed androgen treatment. The extreme severity of the disease, the high risk for siblings and the impossibility of prenatal diagnosis determine the recommendations for limiting childbearing or artificial insemination.

The X-linked form of congenital adrenal hypoplasia is often combined with glycerol kinase deficiency – congenital familial hypocorticism with glyceroluria. In this case, already a few days after birth, severe hypocorticism develops – with hypoglycemia, collapse and exicosis. The syndrome is highly latent, however, in the case of early use of intensive replacement therapy, survival with the development of mental retardation, growth retardation, strabismus, myopathy and osteoporosis with pathological fractures is possible.

The diagnosis is confirmed by laboratory parameters characteristic of primary hypocorticism, as well as hyperglycerolemia, hyperlipidemia, hyperammonemia, glyceroluria and hyperoroticouria.

Wolman's disease. The disease is associated with a mutation in the gene responsible for the synthesis of cholesterol esterase – lysosomal acid lipase. The latter releases cholesteryl esters from lipid droplets localized in the adrenal glands and maintains the level of free cholesterol necessary for the synthesis of corticosteroids. The cholesterol esterase gene is located on chromosome 10q.

Wolman's disease is the result of the accumulation of cholesterol esters and triglycerides, which are found in the lysosomes of almost all tissues (not just the adrenal glands): in the liver, spleen, lymph nodes, bone marrow, small intestine, central nervous system, retina, thymus and other organs. The symptom complex characteristic of the disease includes hypocorticism, which manifests itself from the first weeks of life; hepatosplenomegaly, xanthomatosis, intestinal malabsorption, adrenal calcification.

Children are born hypotrophic. From the first weeks of life, they experience constant vomiting and diarrhea, physical development is delayed, and there is no weight gain. The death of patients often occurs in the first half of life.

Laboratory tests determine: hyponatremia and hyperkalemia, decreased levels of cortisol in the blood and urine with increased levels of corticotropin. The diagnosis is confirmed by bone marrow aspiration. The foam cells found in it contain large lysosomal vacuoles filled with cholesterol esters. A similar picture is observed in fibroblasts and leukocytes.

The disease is inherited in an autosomal recessive manner. The high genetic risk for siblings of patients and the severity of the pathology serve as the basis for prenatal diagnosis in subsequent pregnancies by determining a decrease in enzyme activity.

The described genetic syndromes represent clinical varieties of total primary CAI. Congenital and hereditary forms of partial primary hypocorticism are also distinguished. These are various variants of enzymatic disorders with salt-wasting syndrome: cholesterol desmolase deficiency, 3β-ol-steroid dehydrogenase deficiency and salt-wasting form of 21-hydroxylase deficiency, 2 types of hypoaldosteronism and 3 types of pseudohypoaldosteronism. The genetically determined diseases presented below are variants of secondary hypocorticism.

ACTH SYNTHESIS DEFECT

The disease is based on a decrease in the production of GCs and sex steroids, caused by a hereditary defect in the synthesis of corticotropin. At the same time, the synthesis of mineralocorticoids is maintained, which is only to a small extent regulated by ACTH.

An isolated loss of glucocorticoid synthesis causes hypoglycemia, the leading clinical manifestation of the disease. Since the enzyme that catalyzes the conversion of norepinephrine to adrenaline, phenylethanolamine-N-methyltransferase, is activated by GCs, a deficiency of the latter is associated with a decrease in the formation of adrenaline, which aggravates the severity of hypoglycemic conditions.

The disease is rare; its mode of inheritance is autosomal recessive. It manifests itself from the first days of life as repeated severe hypoglycemic conditions. As with other clinical forms of secondary hypocorticism, melasma and salt-wasting syndrome are absent. The syndrome is highly lethal, but there are also mild variants of its clinical course.

The scope of diagnostically significant laboratory tests (assessment of blood levels of ACTH, cortisol, functional test parameters), treatment tactics (GC replacement therapy) are the same as for other variants of secondary hypocorticism.

The genetic risk for siblings is high, but replacement therapy prescribed from the first days of life improves the prognosis.

Corticotropin deficiency is accompanied by many congenital and hereditary conditions characterized by disruption of the structure and function of the hypothalamic-pituitary formations – hypoplasia and ectopia of the pituitary gland, anencephaly, craniopharyngioma, abnormalities of the sella turcica, etc. However, hypocorticism is not the leading clinical manifestation and, as a rule, is determined only when targeted examination.

As an example, let us cite such a well-known disease as pituitary dwarfism (panhypopituitary dwarfism), caused by a deficiency of somatotropic and other pituitary hormones. In patients with pituitary dwarfism, clinical manifestations of adrenal insufficiency, as a rule, are not observed, however, in stressful situations, the development of Addisonian crisis is possible.

Laboratory tests reveal a decrease in the concentration in the blood of all tropic hormones of the pituitary gland. The level of cortisol in the blood does not go beyond normal limits, however, the daily excretion of free cortisol in the urine is reduced.

Glucose tolerance is reduced, insulin administration causes deeper and longer-lasting hypoglycemia than in healthy people, as demonstrated by a clinical case of diabetes in a patient with pituitary dwarfism.

Congenital ACTH resistance syndrome

The symptom complex includes the early (from the first months of life) appearance of hypoglycemic conditions, often accompanied by convulsions, which is provoked by infectious diseases. Sometimes the disease manifests itself at 3–5 years of age. Hyperpigmentation of the skin increases, general weakness and other signs of adrenal insufficiency develop, the body's resistance to infections and other stress factors decreases, which can provoke an adrenal crisis.

The disease is inherited in an autosomal recessive manner and is usually caused by inactivating mutations in the ACTH receptor gene. In some patients such mutations are not detected. In these cases, the cause of the syndrome is mutations in other genes that disrupt intracellular ACTH signal transmission. Laboratory examination reveals a sharp increase in ACTH levels in the blood; at the same time, the level of cortisol is reduced and does not increase under test conditions with corticotropin. The mineralocorticoid function of the adrenal

cortex is preserved – aldosterone levels and electrolyte parameters are normal in most patients, which must be taken into account in differential diagnosis with other forms of hypocorticism. A biopsy of the adrenal cortex reveals hypoplasia or aplasia of the zona fasciculata and reticularis.

Allgrove syndrome (congenital familial hypocorticism with glyceroluria) is also inherited autosomal recessively and, in addition to ACTH resistance, includes achalasia of the cardiac esophagus and impaired lacrimation – alacrymia. The name «three A syndrome» was given by the letters of the names of the main components of the syndrome. Typical clinical symptoms – hyperpigmentation, severe attacks of hypoglycemia in childhood (sometimes fatal), include neurological disorders, mental retardation, hyperkeratosis of the palms and soles.

Mutations of the ACTH receptor gene were not identified, but linkage to some genes on 12 q13 was detected.

Laboratory examination is similar to the above-described syndrome of isolated ACTH deficiency.

Glucocorticoid replacement therapy is used to treat patients with ACTH resistance.

A high genetic risk for siblings of patients and the impossibility of prenatal diagnosis suggest a limitation in childbearing. Siblings of patients should be registered at a dispensary and examined to identify hormonal disorders and timely prescribe replacement therapy.

HYPOALDOSTERONISM

A decrease in the functional activity of the zona glomerulosa of the adrenal glands (hypoaldosteronism) is associated with numerous clinical manifestations of adrenal insufficiency – loss of sodium, hypovolemia, arterial hypotension, etc. Usually, aldosterone deficiency is combined with a deficiency of cortisol and other steroid hormones synthesized in the adrenal cortex. Clinical syndromes caused by isolated hypoaldosteronism or selective insufficiency of aldosterone secretion are also described – with the intact functional state of the zona fasciculata and reticularis of the adrenal cortex.

Congenital hypoaldosteronism associated with enzyme deficiency

Congenital hypoaldosteronism is based on a deficiency of the P450 enzyme with 11B2, which catalyzes the final stages of aldosterone synthesis, caused by a mutation in the CYP11B2 gene. In addition to 11β-hydroxylase, which converts deoxycorticosterone into corticosterone, this enzyme has 18-hydroxylase and 18-oxidase activities. Under the action of the P450 enzyme with 11B2, corticosterone is successively converted into 18-hydroxycorticosterone and aldosterone. As noted, the latter two activities are called corticosterone methyl oxidase type I and type II, respectively (CMO I and CMO II). In both variants of the enzymatic defect, along with excess production of corticosterone, renin activity increases. Corticosterone synthesis continues due to the continued

activity of the P450 enzyme with 11B1, which catalyzes the 11β-hydroxylation of deoxycorticosterone. In patients with reduced CMO I activity, the levels of 18-hydroxycorticosterone in the blood and its metabolites in the urine are reduced, while in the more common CMO II, the production of 18-hydroxycorticosterone is increased. The production of cortisol under conditions of deficiency of the P450 enzyme with 11B2 is not impaired, so adrenal hyperplasia does not develop.

This disease was first described in 1964. Called Visser-Cost syndrome in some publications, it is rare in the general population, but is diagnosed with increased frequency among Jews of Iranian origin. Establishing the incidence of cases is significantly complicated by the fact that the formation of extra-adrenal mechanisms of sodium retention with age can lead to an asymptomatic course of the disease in adults.

Hypoaldosteronism

The disease clinically manifests itself in newborns or infancy.

From the first days of life, the child experiences regurgitation and/or vomiting, anorexia, excicosis, weight loss, constipation, unmotivated rises in temperature, and later growth retardation becomes noticeable. Diarrhea and infectious diseases often worsen the child's condition. The severity of symptoms of hypoaldosteronism may vary; as a rule, patients' condition improves with age. It is noted that the later the disease manifests itself, the milder its form and the better the prognosis. In rare cases, late manifestation of isolated hypoaldosteronism is observed in people over 40 years of age, mainly in men. There is no salt-wasting syndrome, but cardiovascular disorders develop due to severe hyperkalemia. Congenital hypoaldosteronism is differentiated from diseases of various etiologies, with manifestations of salt-wasting syndrome. For differential diagnosis with salt-wasting forms of congenital dysfunction of the adrenal cortex, the normal structure of the external genitalia is essential. The diagnostic difference between isolated hypoaldosteronism is the adequate response of the glucocorticoid function of the adrenal cortex in response to a test with corticotropin.

Laboratory indicators confirming the diagnosis of isolated hypoaldosteronism include: a sharp decrease in aldosterone levels (up to undetectable); hyponatremia; hyperkalemia, metabolic acidosis; increased renin content – in combination with normal levels of corticotropin, cortisol and androgens of the adrenal cortex. A particularly valuable diagnostic criterion is a significant increase in the corticosterone/aldosterone ratio. To assess the degree of defect in aldosterone synthesis, it is necessary to determine the level of 18-hydroxycorticosterone, which decreases in patients with type I hypoaldosteronism and increases in type II disease.

Therapeutic tactics in children consist of the additional administration of large quantities of refined salt (for newborns – up to 5 g per day) and the appointment of mineralocorticoids. In the future, the issue of prescribing mineralocorticoids and introducing additional salt into the diet is decided individually, taking into account clinical and laboratory parameters.

The disease is familial and is inherited in an autosomal recessive manner. The genetic risk for siblings is high, but early diagnosis and effective treatment can almost completely rehabilitate patients. The clinical syndrome of isolated hypoaldosteronism with generalized or partial enzymatic deficiency can be acquired, combined with polyendocrine autoimmune deficiency, including autoimmune thyroiditis and idiopathic hypoparathyroidism.

A defect in aldosterone biosynthesis can be induced by long-term use of a number of pharmacological drugs – heparin, indomethacin, licorice preparations, β-blockers, veroshpirone. The latter, acting directly on the zona glomerulosa, increases sodium excretion, which may override the renin-angiotensin stimulating effect of the drug.

Hypoaldosteronism observed after removal of aldosteroma is associated with profound inhibition of the renin-angiotensin system as a result of prolonged hypersecretion of aldosterone. By prescribing large doses of veroshpiron in the preoperative period, it is possible to restore the sensitivity of the reninangiotensin system.

In addition to primary isolated hypoaldosterinism, its secondary forms are observed, associated with insufficient production of renin by the kidneys or the release of inactive renin – hypereninemic hypoaldosteronism. In this form of pathology, plasma renin activity and aldosterone production are weakly stimulated by orthostatic load, sodium restriction in the diet, and diuretics. This group is heterogeneous in pathogenesis and, along with independent clinical variants, hyporeninemic hypoaldosteronism often complicates the course of such diseases: diabetes mellitus, chronic nephritis with renal tubular acidosis and impaired renal function.

Hyperreninemic hypoaldosteronism is sometimes observed in sepsis and major blood loss, since hypoxia inhibits the activity of enzymes necessary for the synthesis of aldosterone.

Pseudohypoaldosteronism

Pseudohypoaldosteronism includes diseases based on impaired sensitivity of target tissue cells to mineralocorticoids. There are pseudohypoaldosteronism types 1 and 2 (PsHA-1 and PsHA-2). PsHA-1 is divided into 2 subtypes – with autosomal recessive and dominant types of inheritance.

The development of **PsHA-1 with autosomal recessive inheritance** is associated with defects in genes encoding one of the three subunits of the epithelial sodium channel – SCNN1A, SCNN1B, SCNN1G. Epithelial sodium channel subunits are expressed in the apical membrane of epithelial cells lining the distal nephron, respiratory tract, colon, sweat and salivary gland ducts. With their defects, the functions of the epithelium in these organs change, as a result of which the reabsorption of sodium and chlorides is disrupted, and potassium retention is observed.

The disease usually manifests itself soon after birth and is manifested by severe salt loss syndrome – regurgitation, weight loss, vomiting, dehydration, delayed physical development; arterial hypotension is characteristic, and vascular collapse is possible. Violation of the secretory function of the epithelium and respiratory tract is often manifested by respiratory infections.

Laboratory tests reveal: hyponatremia, hypokalemia, metabolic acidosis, increased urinary sodium excretion. An increase in blood aldosterone levels is characteristic against the background of high plasma renin activity, with normal levels of cortisol and ACTH in the blood. The diagnosis is confirmed by identifying mutations in one of the epithelial sodium channel subunit genes.

Mineralocorticoid replacement therapy is ineffective. The loss of salt can be compensated with large doses of refined salt – 1,2–2,4 g/kg/day, which are selected individually according to clinical and laboratory parameters. The need for refined salt in newborns is up to 5 g per day; in children of the first two years of life, the required amount of sodium chloride varies from 8 to 12 g per day. Treatment is lifelong, but with age, the need for refined salt may decrease.

PsHA-1, with an autosomal dominant pattern of inheritance, is associated with defects in the NR3C 2 gene, which encodes the mineralocorticoid receptor, which is expressed predominantly in the distal nephron. The disease is caused by a decrease in renal sodium reabsorption and manifests itself as salt-wasting syndrome. The severity of clinical symptoms can vary – from severe forms to asymptomatic variants, detected only during laboratory examination.

In manifest forms of the disease the following is detected:

- increased level of aldosterone – against the background of high plasma renin activity;
- electrolyte disturbances – hyponatremia, hyperkalemia;
- metabolic alkalosis;
- increased urinary sodium excretion.

In the asymptomatic course of the disease, only changes in the hormonal profile may differ: increased levels of aldosterone in the blood, hyperreninemia.

A unified treatment strategy has been developed for patients with PsHA-1 autosomal dominant and PsHA-1 autosomal recessive types of inheritance.

Pseudohypoaldosteronism type 2 (PsHA-2) is also known as Gordon's syndrome or familial hyperkalemia and hypertension. This relatively rare disease with an autosomal dominant pattern of inheritance is associated with an isolated defect in potassium transport in the distal renal tubules. It is characterized by hypertension, hyperkalemia, hyperchloremia and metabolic acidosis with normal glomerular function and reduced plasma renin levels. The disease is combined with a violation of the loci of two chromosomes – 1q31-42 and 17 p 11-q21.

Administration of mineralocorticoids does not restore electrolyte balance. Treatment of PsHA-2 consists of furosemide, desmopressin and sodium bicarbonate, which allows control of both hyperkalemia and hyperchloremic acidosis, as well as hypertension.

ACUTE ADRENAL INSUFFICIENCY

Acute adrenal insufficiency (AAI) /hypoadrenal crisis/ – an emergency condition that occurs as a result of a sharp decrease in the production of hormones by the adrenal cortex, clinically manifested by severe adynamia, vascular collapse, and gradual loss of consciousness.

Etiology

Adrenal or Addisonian crises develop more often in patients with primary or secondary damage to the adrenal glands. However, they can occur in patients without previous adrenal diseases. The development of Addisonian crisis may be the first manifestation of the disease *in latent Addison's disease (primary chronic adrenal insufficiency (CAI)), Schmidt's syndrome.*

AAI is a threatening condition in patients with *bilateral adrenalectomy* performed in connection with Itsenko-Cushing's disease and other conditions. Lack of compensation for CAI in this group of patients due to inadequate replacement therapy, mental and physical stress, minor and major operations, cooling, etc. can lead to the development of severe adrenal crises. Decompensation of adrenal insufficiency most often occurs in patients with *Nelson's syndrome*.

Diseases in which Addisonian crises are possible include *congenital adrenal cortex dysfunction and isolated insufficiency of aldosterone secretion.* In children and adults with the salt-wasting form of congenital adrenal cortex dysfunction, AAI can occur during intercurrent illnesses and in extreme conditions.

The development of AAI during stressful situations can occur with secondary adrenal insufficiency – diseases of the hypothalamic-pituitary origin, exogenous administration of corticosteroids for non-endocrine diseases. A special group of patients potentially susceptible to AAI are patients previously treated with GCs for non-endocrine diseases. As a result of long-term use of glucocorticoid drugs, the function of the hypothalamic-pituitary-adrenal system is reduced, and during surgical, infectious or other stress, failure of the function of the adrenal cortex is revealed.

Sometimes the cause of AAI is the use of drugs that disrupt the synthesis of adrenal hormones (ketoconazole or mitotane) or accelerate the breakdown of these hormones (rifampicin or phenytonin).

Manifestations of AAI can develop in patients without a previous pathological process in the adrenal glands. Thus, AAI, caused by thrombosis or embolism of the adrenal veins, is called Waterhouse-Friderichsen syndrome. Hemorrhagic adrenal infarction in this syndrome occurs:

– against the background of meningococcal, pneumococcal, streptococcal bacteremia;

– if affected by the polio virus or other severe septic infection;

– in case of acute disseminated intravascular coagulation syndrome, inadequate treatment with anticoagulants;

– for burn disease;

– when treated with ACTH drugs;

– in pregnant women.

Acute infarctions can occur during heart surgery, surgical treatment of cancer of the stomach and esophagus, with various injuries of both the adrenal glands themselves and with injuries to the chest and abdominal cavity – especially against the background of pre-existing long-term chronic subthreshold stress. Waterhouse-Friderichsen syndrome can occur at any age.

Thus, in newborns, the most common cause of adrenal apoplexy is birth trauma (most often during breech birth), followed by infectious and toxic factors. In children in the first 3 years of life, Waterhouse-Friderichsen syndrome can develop even when exposed to minor exogenous factors (acute respiratory viral infections, infectious diseases, stress, etc.). This situation is explained by the anatomical and physiological immaturity of the adrenal glands in this age period.

Pathogenesis

There is an opinion that AAI is a form of manifestation of a violation of the general adaptation syndrome – due to severe stress and overstrain of the hypothalamic-pituitary-adrenal system. That is, an adrenal crisis is caused by a rapid (lightning-fast) decrease or cessation of the secretion of hormones from the adrenal cortex.

In case of AAI, due to the lack of synthesis of gluco- and mineralocorticoids by the adrenal cortex, there is *a loss of sodium and chloride ions in the urine and a decrease in their absorption in the intestine, which leads to dehydration* of the body due to the loss of extracellular fluid and the secondary transition of water from the extracellular space into the cell. Due to severe dehydration, blood volume decreases, which leads to shock. Fluid loss also occurs through the gastrointestinal tract. Indomitable vomiting and frequent loose stools indicate severe disturbances in the electrolyte balance in the body.

Disorders of potassium metabolism are involved in the pathogenesis of AAI. In the absence of adrenal hormones, potassium levels in the serum, intercellular fluid, and cells increase. In conditions of adrenal insufficiency (aldosterone deficiency), the excretion of potassium in the urine decreases, since the excretion of potassium by the distal convoluted tubules of the kidneys is impaired. *Excess potassium* in the heart muscle leads to impaired myocardial contractility, which can in turn lead to local changes. With AAI, the functional reserves of the myocardium decrease.

Under AAI conditions, carbohydrate metabolism is disrupted in the body: *the level of glucose in the blood decreases, glycogen reserves in the liver and skeletal muscles decrease, and sensitivity to insulin increases.* With insufficient secretion of GCs, the synthesis and metabolism of glycogen in the liver is impaired. In response to hypoglycemia, glucose is not released in the liver. GCs stimulate gluconeogenesis in the liver – from proteins, fats and other precursors, which leads to normalization of carbohydrate metabolism.

Clinical manifestations of hypoglycemia accompany AAI; in some cases, as a result of a severe deficiency of glucose in the tissues, hypoglycemic coma

develops. With a lack of GCs, the level of urea, the end product of nitrogen metabolism, decreases. The effect of GCs on protein metabolism is not only catabolic or anti-anabolic – it is much more complex and depends on many factors.

AAI is characterized by a *decrease in renal function*, expressed in an increase in the content of non-protein nitrogen, a decrease in the glomerular filtration rate, and an impairment of the ability of the tubules to absorb water and electrolytes.

According to modern concepts, the pathogenetic basis of Waterhouse-Friderichsen syndrome is considered to be bacterial shock, leading to acute vascular spasm, necrosis and hemorrhages in the cortex and medulla of the adrenal glands. Lesions of the adrenal glands in this syndrome can be focal and diffuse, necrotic and hemorrhagic. The most typical mixed form of Waterhouse-Friderichsen syndrome is necrotic-hemorrhagic. More often, changes are observed in two adrenal glands; less often, one adrenal gland is affected.

Clinical manifestations

Below are the most characteristic *clinical signs* of AAI:

- nausea;
- vomit;
- severe muscle weakness;
- high temperature;
- palpitations, pain in the heart area, collapse;
- diarrhea;
- stomach ache;
- mental disorders.

The severity of individual symptoms is variable, which causes a variety of clinical forms of crisis. *The leading clinical symptom* of AAI is a significant decrease in BP, which is often in the nature of collapse and cardiovascular shock, resistant to standard anti-shock therapy. In particular, Addisonian collapse is not eliminated by the introduction of catecholamines, which further indicates the absence of their deficiency even with total adrenalectomy. Such inherent AAI symptoms as acrocyanosis, profuse sweat, coldness of the extremities, hyperthermia, some abdominal and mental symptoms are to a certain extent associated precisely with an increase in the activity of the sympathoadrenal system.

The development of abdominal symptoms of AAI begins with a disturbance of appetite: from its complete loss to an aversion to food and even its smell. Then nausea and vomiting occurs. As the crisis progresses, vomiting becomes uncontrollable and loose stools appear. Repeated vomiting and diarrhea quickly lead to dehydration. Abdominal pain occurs, often of a diffuse spastic nature. Sometimes a picture of an acute abdomen appears with symptoms characteristic of acute appendicitis, pancreatitis, cholecystitis, perforated ulcers, and intestinal obstruction.

Quite often, such patients develop acute hemorrhagic gastroenteritis, accompanied by tension in the anterior abdominal wall, «coffee grounds» vomiting, and melena – a typical picture of acute gastrointestinal bleeding. If

such a picture of AAI develops after surgery, there is a real threat of relaparotomy. An error in diagnosis in patients with Addisonian crisis and surgical intervention can be fatal for them.

During the development of the Addisonian crisis, *neuropsychic disorders* appear: epileptic convulsions, meningeal symptoms, delusional reactions, lethargy, impaired consciousness, stupor. Brain disorders that occur during Addisonian crisis are caused by cerebral edema, electrolyte imbalance, and hypoglycemia. Relief of convulsive epileptic seizures with mineralocorticoid drugs in patients during acute hypocorticism provides a better therapeutic effect than various anticonvulsants. An increase in plasma potassium content in patients with AAI leads to impaired neuromuscular excitability. Clinically, this manifests itself in the form of paresthesia, conduction disorders of superficial and deep sensitivity. Muscle cramps develop as a result of a decrease in extracellular fluid. Mental disorders vary widely both in form and in depth (lethargy, stupor, hallucinations, delirium, coma), so patients with AAI are often mistakenly diagnosed with manic or paranoid psychosis, toxic syndrome, cerebral coma, etc.

Clinical manifestations of a crisis usually go through *three successive stages:*

Stage 1 – increased weakness and hyperpigmentation of the skin and mucous membranes (with primary CAI; headache, loss of appetite, nausea and decreased BP. A feature of hypotension in AAI is the lack of compensation from hypertensive drugs – BP increases only in response to the administration of GCs and mineralocorticoids.

Stage 2 – severe weakness, chills, severe abdominal pain, hyperthermia, nausea and repeated vomiting with severe signs of dehydration, oliguria, palpitations, progressive decrease in BP.

Stage 3 – coma, vascular collapse, anuria and hypothermia.

In patients with sudden dysfunction of the adrenal glands as a result of hemorrhage, necrosis, clinical symptoms of acute hypocorticism can develop without precursors. The duration of an Addisonian crisis can vary from several hours to several days and is determined by a number of factors: the severity of adrenal insufficiency; the reasons that led to the crisis; the general condition of the body and the time of administration of hormonal therapy.

Clinical manifestations of AAI, which develop in children and adults *without previous disease of the adrenal cortex*, have a number of features. The development of clinical symptoms in Waterhouse-Friderichsen syndrome depends on the degree of destruction of the adrenal cortex.

Acute massive hemorrhage into the adrenal glands is accompanied by a sudden collaptoid state. BP progressively decreases, a petechial rash appears on the skin, body temperature rises, and signs of acute heart failure occur – cyanosis, shortness of breath, rapid small pulse. Sometimes the leading symptom is severe abdominal pain, often in the right half or umbilical region. The nature of the pain can be very severe. In some cases, symptoms of internal bleeding occur.

In case of AAI, in addition to the symptoms characteristic of a crisis, organic disorders are always noted that became the causes of its occurrence: operational stress, infections (usually pneumonia, bronchitis, etc.).

Diagnosis

Anamnestic indications of previous episodes of adrenal disease are important for making the diagnosis of AAI. A history of tuberculosis in any organs may indirectly indicate tuberculous damage to the adrenal glands. If the patient has another autoimmune disease (thyroiditis, diabetes mellitus, systemic connective tissue diseases), autoimmune Addison's disease can be assumed. For the diagnosis of AAI, an important symptom is ***increased pigmentation of the skin*** and mucous membranes, severe ***hypotension***, which cannot be corrected by the administration of vasoconstrictor drugs. In some patients, melasma is not clearly expressed and is represented by small signs: increased pigmentation of the nipples, palmar lines, an increase in the number of pigment spots, moles, darkening of postoperative sutures.

In primary CAI, increased pigmentation at the time of decompensation against the background of progressive hypotension contributes to the diagnosis of Addisonian crisis. It is much more difficult to suspect adrenal insufficiency in depigmented forms, the so-called «white Addisonism». The absence of melasma with primary hypocorticism occurs in approximately 10 % of patients and in all with secondary adrenal insufficiency. Hyperpigmentation is also characteristic of patients with congenital dysfunction of the adrenal cortex. It is associated with an increase in ACTH secretion – in response to decreased cortisol production.

Anamnestic data help to diagnose secondary adrenal insufficiency:

– about previous diseases or injuries of the central nervous system;

– about operations on the pituitary gland or radiation therapy to the hypothalamic-pituitary region;

– about taking GCs for various autoimmune diseases.

Laboratory methods for diagnosing AAI are quite limited. Determination of plasma cortisol, aldosterone and ACTH levels takes time. In addition, a single indicator of hormone levels does not fully reflect the functional state of the adrenal cortex. Diagnostic tests used for CAI are contraindicated in acute Addisonian crisis. The diagnosis of AAI is established on the basis of the typical clinical picture of the disease and the dynamics of changes in electrolyte balance.

During Addisonian crisis and dehydration, the sodium and chloride content in the blood serum decreases. Sodium levels drop to 130 mEq/L or lower. Characterized by a decrease in sodium excretion in the urine, which is less than 10 g per day.

An important indicator for the diagnosis of AAI is ***hyperkalemia*** up to 5–6 meq/l, sometimes this figure reaches 8 meq/l. As a result of an increase in potassium content in the blood and a decrease in sodium, the Na/K ratio

changes. If in healthy people this coefficient is 32, then in acute hypocorticism it is characterized by a decrease to 20 or lower. Hyperkalemia has a toxic effect on the myocardium; on the ECG this is manifested by a high, pointed Q wave, as well as slow conduction. In conditions of insufficiency of adrenal cortex function, the following can be detected: prolongation of the ST interval and QRT complex and low-voltage ECG.

In addition to significant loss of water and salts, **hypoglycemia** poses a serious danger to patients during Addisonian crisis. Determination of blood glucose should be carried out under treatment supervision. A hypoglycemic crisis can also be an independent manifestation of decompensation of CAI – during fasting and infectious diseases. During acute hypocorticism, blood glucose levels decrease, but sometimes there are no hypoglycemic manifestations.

Loss of sodium and water during a crisis leads to true *blood thickening and an increase in hematocrit.* If blood thickening does not depend on adrenal insufficiency, but is caused by diarrhea and vomiting, the concentration of sodium and chlorides may be normal, increased or decreased, and the potassium content under these conditions never increases. With the development of AAI, the level of urea and residual nitrogen often increases significantly, and varying degrees of *acidosis* occur, as evidenced by a decrease in blood alkalinity.

Treatment

In case of AAI, urgent prescription of replacement therapy with glucocorticoid and mineralocorticoid drugs and measures to remove the patient from a state of shock are necessary. Treatment started at the first signs of AAI provides more opportunities to bring the patient out of the crisis. The most life-threatening conditions are the first days of acute hypocorticism!

In medical practice, there is no difference between a crisis that occurs during an exacerbation of Addison's disease after removal of the adrenal glands and a coma that occurs as a result of acute destruction of the adrenal cortex in other diseases.

In case of AAI, ***preference is given to hydrocortisone drugs*** (*Table 6*).

Table 6

Treatment of acute adrenal insufficiency

Events	Notes
1. Hydrocortisone sodium succinate – 100–150 mg intravenously over 5 minutes	
2. Hydrocortisone sodium succinate 300 mg for 24 hours (100 mg in the first two hours) in saline solution or 5 glucose solution intravenously drip	• The need for hydrocortisone, depending on the patient's condition, on the first day can reach up to 1–1,5 • On the second day, 150 mg of hydrocortisone sodium succinate is usually administered, on the third – 75 mg
3. Simultaneously with the intravenous administration of hydrocortisone sodium succinate, *hydrocortisone acetate* is prescribed - in the form of a suspension of 50–75 mg intramuscularly every 4–6 hours on the first day	

Events	Notes
4. Intravenous infusion of 0,9% NaCl solution and 5 % glucose solution until dehydration and hyponatremia are eliminated	• On the first day, up to 3 liters of fluid are administered (0,9 saline solution, 5% glucose solution). • Infusion therapy is stopped when BP stabilizes at 110/70 mmHg

The administration of hydrocortisone preparations is prescribed intravenously by stream and drip, for this purpose preparations of hydrocortisone sodium succinate are used. For intramuscular administration, hydrocortisone acetate preparations are used in the form of a suspension. In acute adrenal crisis, all three methods of administering hydrocortisone are usually combined.

- Begin by prescribing 100–150 mg of hydrocortisone sodium succinate intravenously stream. The same amount of the drug is dissolved in 500 ml of isotonic sodium chloride solution and 5 % glucose solution with the addition of 50 ml of 5 % ascorbic acid and administered intravenously drip over 3–4 hours at a rate of 40–100 drops per minute.
- Simultaneously with the intravenous administration of water-soluble hydrocortisone, a suspension of hydrocortisone is administered intramuscularly at 50–75 mg every 4–6 hours. The dose depends on the severity of the condition and is adjusted taking into account the results of increased BP and normalization of electrolyte disturbances.
- During the first day, the total dose of hydrocortisone is 400–600 mg, less often – 800–1000 mg, sometimes more. Intravenous administration of hydro-cortisone is continued until the patient recovers from collapse and BP rises above 100 mm Hg. and continue its intramuscular administration 4–6 times a day at a dose of 50–75 mg with a gradual reduction in dose to 25–50 mg and increasing intervals of administration 2–4 times a day for 5-7 days. Then patients are transferred to oral treatment with prednisolone at a dose of 10–20 mg per day, additionally prescribing hydrocortisone sodium succinate 30 mg per day or cortisone acetate at a dose of 25–50 mg per day.
- Along with the administration of GCs, therapeutic measures are carried out to combat dehydration and shock. The amount of isotonic sodium chloride solution and 5 % glucose solution on the first day is 2,5–3,5 liters. In case of repeated vomiting, intravenous administration of 10–20 ml of 10 % sodium chloride solution is recommended at the beginning of treatment, and repeated administration in case of severe hypotension and anorexia. After relief of the symptoms of gastrointestinal dyspepsia – nausea, vomiting – the patient is prescribed oral fluid intake.
- In addition to an isotonic solution of sodium chloride and glucose, if necessary, rheopolyglucin is prescribed in a dose of 400 ml.
- Treatment with gluco- and mineralocorticoids should be carried out in adequate quantities under the control of sodium, potassium and glucose levels

in the blood and BP. The insufficient effectiveness of treatment for Addisonian crisis may be associated with a low dose of glucocorticoid drugs or salt solutions, with a rapid reduction in the dosage of drugs.

The use of prednisolone or dexamethasone compensates for the deficiency of gluco-, but not mineralocorticoids. In case of severe dehydration – against the background of acute insufficiency – you cannot limit yourself to its administration alone!

Complications of hormonal therapy are associated with drug overdose. The most common is edematous syndrome (swelling of the limbs, face, in cavities), parasthesia, paralysis - associated with hypokalemia. In these cases, potassium chloride is prescribed in solution or powder – up to 4 g per day; for acute hypokalemia, intravenous administration of a 0,5 % solution of potassium chloride in 500 ml of a 5 % glucose solution is indicated.

In cases of cerebral edema, mannitol and diuretics are prescribed. An overdose of GCs is accompanied by the development of symptoms of mental disorders – from mood and sleep disorders to severe anxiety, sometimes accompanied by hallucinations. Reducing the dose of corticosteroids to maintenance levels usually relieves psychiatric symptoms.

In addition to pathogenetic hormonal and infusion therapy, etiotropic treatment is carried out aimed at eliminating the cause of AAI – antitoxic, antishock, hemostatic, antibacterial therapy, etc. *Symptomatic* treatment consists of prescribing cardiotropic, analeptic, sedative and other drugs according to indications.

Prevention. To prevent the progression of the crisis, it is important to promptly recognize and prescribe treatment for initial or subacute adrenal insufficiency. The development of precursors of crisis or acute hypocorticism can be prevented in patients with CAI during major and minor surgical interventions, infectious processes, during pregnancy and childbirth.

<u>*For preventive purposes*</u>, patients are prescribed parenteral administration of hydrocortisone in doses lower than during Addisonian crisis.

• The day before surgery, hydrocortisone is administered intramuscularly at a dose of 25–50 mg 2–4 times a day.

• On the day of surgery, the dose of the drug is increased 2–3 times. During surgery, 100–150 mg of hydrocortisone is administered intravenously drip and 50 mg of hydrocortisone is administered intramuscularly every 4–6 hours for 1–2 days.

• Parenteral administration of hydrocortisone is continued after surgery for 2–3 days.

Then they are gradually transferred to replacement therapy with prednisolone, hydrocortisone or cortisone and fludrocortisone per os. At first, the dose is higher than usual, the duration depends on the general condition of the patient. When the severity of surgical stress is eliminated, the patient is transferred to the doses of drugs used before surgery.

TESTS

1. A 45-year-old patient with the history of Addison's disease since childhood, became nervous and restless due to a stressful situation. On examination the patient is pale, cold, his pulse is 115/min., blood pressure is 65/30 mm Hg. Which of the following complications developed in this patient?

A. Cardiac tamponade.
B. Morganhi-Adams-Stokes syndrome.
C. Thyrotoxic crisis.
D. Acute adrenal insufficiency.
E. Acute myocardial infarction

2. A 53-year-old patient with a history of tuberculosis notes pronounced general weakness, the appearance of cyanosis, abdominal pain, nausea, sometimes vomiting, the smell of acetone from the mouth, hyperpigmentation of skin folds. On examination his blood pressure is 75/40 mm Hg., pulse is 120/min. Blood chemistry test shows: sodium – 127 mmol/l, chlorides – 75 mmol/l, potassium – 5,8 mmol/l, glucose – 3,9 mmol/l, urea – 16 mmol/l; in urine: protein – 0,67 g/l, leukocytes – 8–10 in the FOV, erythrocytes – 7–8 in the FOV, cylinders – in some places. In order to clarify the diagnosis, which of the following investigations should be done?

A. Blood cortisol concentration.
B. Blood creatinine concentration.
C. Blood glucosuric profile.
D. Blood concentration of ALT, AST.
E. Urine concentration of ketone bodies.

3. A 53-year old patient with the history of bronchial asthma and glucocorticoids administration lost consciousness after training in the gym. His blood pressure is 45/20 mm Hg. Shortly before the development of the above-mentioned condition, he stopped taking his medicines. On examnation his heart sounds are muffled, pulse is 100/min., weak, rhythmic. His blood glucose level is 3,2 mmol/l, sodium – 117 mmol/l, potassium – 6,0 mmol/l. The preliminary diagnosis is which of the following?

A. Pheochromocytoma.
B. Cardiogenic shock.
C. Status asthmaticus.
D. Acute adrenal insufficiency.
E. Hypoglycemic coma.

4. A 42-year-old patient notes general weakness, weight loss, lack of appetite, nausea, vomiting, abdominal pain. On examination her blood pressure is 70/45 mm Hg, bradycardia, hyperpigmentation of skin. Blood chemistry test shows: decreased blood cortisol concentration, decreased blood aldosterone concentration, the excretion in urine of 17 – KS and 17 –OKS are decreased, hyponatremia, hypochloremia, hypokalemia. What medical measures should be done?

A. Prescribing of glucocorticoids, mineralocorticoids, diet with increased content refined salt.
B. Prescribing of dietary therapy with a high content of refined salt.
C. Prescribing prednisolone.
D. Prescribing aldosterone.
E. Prescribing insulin.

5. Which of the following diseases is characterized by hyperpigmentation of the skin?

A. Itsenko-Cushing's disease. *C. Hyperthyroidism.* *E. Porphyria.*
B. Primary adrenal insufficiency. *D. Hypothyroidism.*

6. Which of the following names is acute adrenal insufficiency caused by thrombosis or embolism of the adrenal veins called:

A. Hemolytic uremic. *D. Waterhouse-Friderichsen syndrome.*
B. DIC-syndrome. *E. Conn's Syndrome.*
C. Nelson's syndrome.

7. A 38-year-old patient notes pronounced general weakness, nausea, lack of appetite. He losts weight by 10 kg during the year. On examination his skin is hyperpigmentation, dark skin folds, nipples, blood pressure is 75/50 mm Hg, pulse is 62/min. The preliminary diagnosis is which of the following?

A. Chronic gastritis. *D. Chronic adrenal insufficiency.*
B. Diabetes. *E. Gallstone disease.*
C. Hypopituitarism.

8. Which of the following symptoms typical for Addison's disease ?

A. Pronounced weakness. *D. Digestive disorders.*
B. Bronze color of the skin. *E. All of the above.*
C. Bronze color of the mucous membranes.

9. Which of the following hormones produceds in the fascicular zone of the adrenal cortex?

A. Aldosterone. *C. Progesterone.* *E. Cortisol.*
B. DHEA. *D. Adrenaline.*

10. A 29-year-old patient was brought to the intensive care unit in a serious condition without consciousness. She considers herself sick for the past 5 months, since after a vacation at sea she developed nausea, vomiting, diarrhea, severe weakness, decreased appetite, and lost weight. She was treated in the gastro-enterology department without effect. The condition worsened. In the history of allergic dermatitis, rhinitis, frequent colds. On examination she is asthenic, has dark-colored skin, reduced turgor. In the lungs breathing is vesicular. Heart sounds are deaf, the rhythm is correct, pulse is 116/min., blood pressure is 40/00 mm Hg., anuria. The preliminary diagnosis is which of the following?

A. Anorexia nervosa. *D. Thyrotoxic crisis.*
B. Primary chronic adrenal insufficiency. *E. Hypercorticism.*
C. Addison's crisis.

CORRECT ANSWERS

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

REFERENCES

1. Alexandraki, K. I., & Kaltsas, G. A. (2022). Adrenal insufficiency and pregnancy. *Current Opinion in Endocrinology & Diabetes and Obesity*, 29(3), 277–283. DOI: https://doi.org/10.1097/MED.0000000000000726.

2. Alexandraki, K. I., Sanpawithayakul, K., & Grossman, A. (2022). Adrenal insufficiency. *Endotext.*

3. Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, Briegel J, Carcillo J, Christ-Crain M, Cooper MS, Marik PE, Umberto Meduri G, Olsen KM, Rodgers SC, Russell JA, Van den Berghe G. Guidelines for the Diagnosis and Management of Critical Illness-Related Corticosteroid Insufficiency (CIRCI) in Critically Ill Patients (Part I): *Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Crit Care Med.* 2017 Dec; 45(12):2078–2088.

4. Arai, K., Papadopoulou-Marketou, N., & Chrousos, G. P. (2020). Aldosterone deficiency and resistance. *Endotext.*

5. Bensing, S., Giordano, R., & Falorni, A. (2020). Fertility and pregnancy in women with primary adrenal insufficiency. *Endocrine*, *70*, 211–217.

6. Betterle, C., Presotto, F., & Furmaniak, J. (2019). Epidemiology, pathogenesis, and diagnosis of Addison's disease in adults. *Journal of endocrinological investigation*, *42*, 1407–1433.

7. Bjørklund, G., Pivin, M., Hangan, T., Yurkovskaya, O., & Pivina, L. (2022). Autoimmune polyendocrine syndrome type 1: Clinical manifestations, pathogenetic features, and management approach. *Autoimmunity reviews*, *21*(8), 103135. DOI: https://doi.org/10.1016/j.autrev.2022.103135.

8. Buonocore, F., & Achermann, J. C. (2020). Primary adrenal insufficiency: New genetic causes and their long-term consequences. *Clinical endocrinology*, *92*(1), 11–20. DOI: https://doi.org/10.1111/cen.14109.

9. Desai, P. D., Kargutkar, S., & Nalla, R. (2023). A Unique Presentation of Nelson Syndrome Due to Partial Adrenal Insufficiency Without Bilateral Adrenalectomy. Cureus, 15(8).

10. Dineen, R., Thompson, C. J., & Sherlock, M. (2019). Adrenal crisis: prevention and management in adult patients. *Therapeutic advances in endocrinology and metabolism*, *10*. DOI: 10.1177/2042018819848218.

11. Hahner, S., Ross, R. J., Arlt, W., Bancos, I., Burger-Stritt, S., Torpy, D. J., ... & Quinkler, M. (2021). Adrenal insufficiency. *Nature Reviews Disease Primers*, 7(1), 19.

12. Kumar, R., & Wassif, W. S. (2022). Adrenal insufficiency. *Journal of Clinical Pathology*, *75*(7), 435–442. DOI: http://dx.doi.org/10.1136/jclinpath-2021-207895.

13. Lindsay, D., & Bhatia, K. (2023). Clinical aspects of endocrinology: parathyroid and adrenal cortex disorders. Anaesthesia & Intensive Care Medicine. DOI: https://doi.org/10.1016/j.mpaic.2023.07.010.

14. Lousada, L. M., Mendonca, B. B., & Bachega, T. A. (2021). Adrenal crisis and mortality rate in adrenal insufficiency and congenital adrenal hyperplasia. *Archives of Endocrinology and Metabolism*, *65*, 488–494. DOI: https://doi.org/10.20945/2359-3997000000392.

15. Martin-grace J, Dineen R, Sherlock M, Thompson CJ. Adrenal insufficiency: physiology, clinical presentation and diagnostic challenges. *Clin Chim Acta*. 2020;505:78–91. DOI: 10.1016/j.cca.2020.01.029.

16. Melmed S., Auchus R. J., Goldfine A. B., & Koenig, R. G., Rosen C. J. (2020) WILLIAMS Textbook of. Endocrinology 14th edition. Elsevier.

17. Miró, M. F., Comí, C. C., & Lorenzo, R. G. (2021). Autoimmune polyendocrinopathy. *Medicina Clínica (English Edition)*, *157*(5), 241–246. DOI: https://doi.org/10.1016/j.medcle.2021.08.006.

18. Nisticò, D., Bossini, B., Benvenuto, S., Pellegrin, M. C., & Tornese, G. (2022). Pediatric adrenal insufficiency: challenges and solutions. *Therapeutics and Clinical Risk Management*, 47–60. DOI: https://doi.org/10.2147/TCRM.S294065.

19. Pignatti, E., & Flück, C. E. (2021). Adrenal cortex development and related disorders leading to adrenal insufficiency. *Molecular and cellular endocrinology*, *527*, 111206. DOI: https://doi.org/10.1016/j.mce.2021.111206.

20. Prete, A., & Bancos, I. (2021). Glucocorticoid induced adrenal insufficiency. *Bmj*, *374*.

21. Quinkler, M., Murray, R. D., Zhang, P., Marelli, C., Petermann, R., Isidori, A. M., & Ekman, B. (2021). Characterization of patients with adrenal insufficiency and frequent adrenal crises. *European Journal of Endocrinology*, *184*(6), 761–771. DOI: https://doi.org/10.1530/EJE-20-1324.

22. Rushworth, R. L., Torpy, D. J., & Falhammar, H. (2020). Adrenal crises in older patients. *The Lancet Diabetes & Endocrinology*, *8*(7), 628–639.

23. Saverino, S., & Falorni, A. (2020). Autoimmune Addison's disease. *Best Practice & Research Clinical Endocrinology & Metabolism*, *34*(1), 101379. DOI: https://doi.org/10.1016/j.beem.2020.101379.

24. Shaunak, M., Blair, J. C., & Davies, J. H. (2020). How to interpret a single cortisol measurement. *Archives of Disease in Childhood-Education and Practice*, *105*(6), 347–351. DOI: http://dx.doi.org/10.1136/archdischild-2019-318431.

25. Siampanopoulou, V., Tasouli, E., & Angelousi, A. (2023). Diagnostic strategies in adrenal insufficiency. *Current Opinion in Endocrinology & Diabetes and Obesity*, 30(3), 141–153.

26. Woodcock, T., Barker, P., Daniel, S., Fletcher, S., Wass, J. A. H., Tomlinson, J. W., ... & Vercueil, A. (2020). Guidelines for the management of glucocorticoids during the perioperative period for patients with adrenal insufficiency: guidelines from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK. *Anaesthesia*, 75(5), 654–663. DOI: https://doi.org/10.1111/anae.14963

27. Younes, N., Bourdeau, I., & Lacroix, A. (2021). Latent adrenal insufficiency: from concept to diagnosis. *Frontiers in Endocrinology*, *12*, 720769. DOI: https://doi.org/10.3389/fendo.2021.720769.

Навчальне видання

Кравчун Нонна Олександрівна
Кравчун Павло Павлович
Герасимчук Ульяна Сергіївна

ХРОНІЧНА НАДНИРКОВА НЕДОСТАТНІСТЬ: ПАТОГЕНЕЗ, КЛІНІКА, ДІАГНОСТИКА, ПІДХОДИ ДО ЛІКУВАННЯ

Навчальний посібник для самостійної роботи здобувачів вищої освіти, слухачів курсів післядипломної освіти та лікарів-ендокринологів

Відповідальний за випуск У. С. Герасимчук

Комп'ютерний набір У. С. Герасимчук
Комп'ютерна верстка О. Ю. Лавриненко

Формат А5. Ум. друк. арк. 4,0. Зам. № 24-34374.

Редакційно-видавничий відділ
ХНМУ, пр. Науки, 4, м. Харків, 61022
izdatknmurio@gmail.com, vid.redact@knmu.edu.ua

Свідоцтво про внесення суб'єкта видавничої справи до Державного реєстру видавництв, виготівників і розповсюджувачів видавничої продукції серії ДК № 3242 від 18.07.2008 р.