Ministry of Education and Science of Ukraine
V. N. Karazin Kharkiv National University

MANAGEMENT OF A PATIENT WITH HYPERCORTISOLISM (CUSHING'S DISEASE/SYNDROME, HYPERCORTICISM WITH PREDOMINANT SECRETION OF MINERALOCORTICOIDS, ESTROGENS, ANDROGENS)

Methodical recommendations
for the preparation of students of higher education in the 6th year of study
in the discipline «Internal Medicine»

Electronic resource

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M24

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M24 **Management** of a patient with hypercortisolism (Cushing's disease/syndrome, hypercorticism with predominant secretion of mineralocorticoids, estrogens, androgens) : methodical recommendations for the preparation of students of higher education in the 6th year of study in the discipline «Internal Medicine» [Electronic resource] / compilers T. M. Tykhonova, M. Yu. Gorshunska, N. Ye. Barabash, L. O. Martymianova. – Kharkiv : V. N. Karazin KhNU, 2024. – (PDF 45 с.)

The methodological recommendations outline the main aspects of the management of patients with hypercorticism syndrome, which include diagnosis and differential diagnosis of its individual forms, modern approaches to treatment.

For students of the 6th year to prepare for practical classes in the discipline «Internal Medicine»

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CONTENT

LIST OF CONVENTIONAL ABBREVIATIONS

AH	arterial hypertension
ACTH	adrenocorticotropic hormone
HA	hyperaldosteronism
HC	hypercorticism
HCor	hypercortisolism
DEA	dehydroepiandrosterone
DEA-s	dehydroepiandrosterone sulfate
CT	computed tomography
MRI	magnetic resonance imaging
PHA	primary hyperaldosteronism
CS	Cushing’s syndrome
USD	ultrasound diagnostics
CD	Cushing’s disease
DM	diabetes mellitus
17-KS	17-ketosteroids
17-OCS	17-oxycorticosteroids

1. BASIC KNOWLEDGE, SKILLS, ATTAINMENTS NECESSARY FOR THE TOPIC STUDYING

Names of previous disciplines	Acquired skills
Foreign Language	Be able to work with foreign literature to gain knowledge about modern methods of diagnosis and treatment of endocrine diseases
Medical informatics	Apply modern computer programs and be able to work with them, have statistical methods for processing the results of clinical studies, analyze the results of studies, be able to evaluate and interpret the results of clinical studies given in information sources, be able to work with electronic databases
Human anatomy. Normal physiology. Histology, cytology and embryology	Know the normal anatomy of the pituitary gland and adrenal glands, the structure, function and principles of the hypothalamic-pituitary-adrenal system regulation, the physiological effects of the hormones of the pituitary gland and adrenal cortex, understand and be able to evaluate the influence of the hypothalamic-pituitary-adrenal system on other organs and metabolic processes in the human body .
Pathomorphology. Pathophysiology	Know the typical pathological processes in morpho-functional disorders of the hypothalamic-pituitary-adrenal system: mechanisms of development, changes in the human body, compensatory reactions of the body, the development of connections that have the essence of "cause-effect". To describe and schematically represent the mechanism of development of typical pathological syndromes during the development of adrenal cortex dysfunction in general, and, in particular, under the conditions of its hyperfunction, to be able to justify etiopathogenetic approaches to drug therapy of hypercorticism, taking into account the heterogeneity of this pathology.
Propaedeutics of internal medicine	Conduct a physical examination of patients, analyze the results of basic laboratory and instrumental research methods. To determine the leading symptoms and syndromes in the development of hypercorticism. To be able to carry out a differential diagnosis, in particular certain forms of hypercorticism, justify and formulate a diagnosis on the basis of a physical examination and the data of additional methods.

Pharmacology	Know the basic principles and generally accepted recommendations for the treatment of certain forms of hypercorticism. Be able to navigate in the nomenclature of medicines used in the therapy of patients with hypercorticism. Know the mechanism of action of such medicines, their pharmacodynamics, indications and contraindications for their use. Know the peculiarities of the pharmacological action of these drugs in different categories of patients. Make a reasonable choice of treatment methods, individual drugs and therapy schemes in accordance with the principles of evidence-based medicine, modern domestic and international protocols. Be able to evaluate the effectiveness and safety of pharmacotherapy taking into account the genesis of hypercorticism, the individual characteristics of the patient, the presence of concomitant diseases

The student should know:

- definition of the concept of "hypercorticism" (HC);
- separate clinical forms of HC;
- epidemiology of diseases accompanied by HC syndrome;
- risk factors for the development of HC;
- classification of HC;
- etiology and pathogenesis of HC;
- mechanisms of hormonal and metabolic disorders during the development of HC;
- the clinical picture of diseases accompanied by HC syndrome, their diagnostic criteria;
- laboratory diagnosis of adrenal gland pathology and various variants of HC, namely: hormonal and metabolic markers, indications for conducting and the basis of interpretation of the results of hormonal and biochemical studies and pharmacological tests;

- diagnostic value of imaging research methods (ultrasound, computer tomography (CT), magnetic resonance imaging (MRI)) of the adrenal glands and hypothalamic-pituitary area;
- the choice of the method of HC treatment depending on the genesis of this pathology.

The student should be able to:

- determine the risk factors for the HC development;
- diagnose HC syndrome taking into account its heterogeneity;
- evaluate biochemical and hormonal parameters, results of pharmacological diagnostic tests and imaging research methods;
- determine the nature of multiorgan complications of diseases accompanied by HC syndrome;
- carry out differential diagnosis of various variants of HC as well as HC with other pathologies;
- be able to choose the tactics of treatment of a patient with HC depending on the disease genesis and existing complications;
- evaluate the dynamics of the hormonal and metabolic status of patients against the background of treatment with the necessary correction;
- interact with related specialists (surgeon, neurosurgeon, ophthalmologist) at the stage of establishing a complete diagnosis, choosing a method and tactics of treatment, as well as during long-term observation of a patient with HC.

2. TOPIC CONTENT

2.1. Terms and their definitions.

ACTH-ectopic syndrome is a complex of HC symptoms that develops as a result of excess production of adrenocorticotropic hormone (ACTH) by a tumor of extrapituitary localization.

Viral syndrome – it is a complex of symptoms characterized by the appearance of male features (physique, hair, tone of voice, etc.) in women as a result of an excess level of androgens (male sex hormones) in the blood or their activation.

HC – it is a set of clinical symptoms arising as a result of long-term chronic exposure to corticosteroids excess amount on the body, regardless of the reason for their increase.

Hypercortisolism (HCor)is a complex of symptoms that develops as a result of cortisol level increase in the blood, regardless of the cause of hypercortisolemia.

Exogenous (iatrogenic) HC - a complex of HC symptoms, which develops as a result of taking supraphysiological doses of corticosteroid hormones.

Endogenous HC -it is a complex of clinical symptoms manifestations that reflects excessive secretion of corticosteroids by the adrenal glands as a result of their primary pathology or due to secondary stimulation of the adrenal glands by ACTH as a result of a pituitary tumor or an ACTH-secreting tumor of another location.

Incidentaloma - a tumor of any endocrine organ that is hormonally inactive (does not produce hormones).

Pituitary macroadenoma -it is a benign tumor of adenohypophysis cells, the diameter of which exceeds 10 mm, with the possible development of neighboring structures compression.

Pituitary microadenoma -a benign tumor from the cells of the adenohypophysis, the diameter of which does not exceed 10 mm.

Cushing's syndrome (CS) -in Ukrainian-language literature, the term is used to denote a benign tumor of the adrenal gland that secretes cortisol; in the English-language literature combines the entire complex of HC symptoms.

Subclinical HC -this is a change in laboratory parameters corresponding to HC in patients with a benign neoplasm of the adrenal glands in the absence of clinical manifestations.

Cushing's disease (CD) -it is a neuroendocrine disease caused by chronic overproduction of ACTH by a pituitary tumor. An increase in the secretion of ACTH, in turn, leads to chronic increased cortisol production by the cortex of the adrenal glands and the development of the complex of endogenous HC symptoms.

2.2. Epidemiology of HC and its individual forms

All neoplastic and hyperplastic diseases of the adrenal glands, accompanied by HC syndrome, belong to orphan (rare) endocrine diseases. The most common is HCor, which is associated with excessive secretion of cortisol (hypercortisolemia) and leads to the occurrence of CS or CD.

CS in most cases is exogenous and develops as a result of long-term use of glucocorticoid (cortisol-like) drug therapy in the treatment of another disease, namely: rheumatoid arthritis, systemic lupus erythematosus, asthma, chronic obstructive pulmonary diseases, malignant tumors, leukemia, and others. Steroid therapy, which is effective for these conditions, can commonly cause iatrogenic CS as a side effect of glucocorticoid use.

According to the results of international epidemiological studies, the incidence of endogenous HCor in the world is from 2 to 10 cases per million population per year. According to the abovementioned and the size of the population, 100-130 new cases should be detected in Ukraine annually. At the same time, in Ukraine, the prevalence of CS is 39.1 cases per 1 million people, the incidence of this nosology is 2–3 cases per 1 million; most of them are related

to the detection of a pituitary adenoma during a CT scan of the brain. HCor in Ukraine often remains undiagnosed and is observed:

- 2–5 % of cases – in patients with diabetes mellitus (DM) type 2 against the obesity background, with inadequate control of glycemia;
- 4.8 % – in patients with idiopathic osteoporosis;
- 4 % – in patients with arterial hypertension (AH);
- 0.4 % (1 in 250) – in women with hirsutism.

Endogenous HCor develops only in 10–20% of cases due to primary pathology of the adrenal glands (ACTH-independent HC). The rest (approximately 80 % of endogenous HC cases) is ACTH-dependent. Among all cases of endogenous ACTH-dependent HC, 75–80 % are caused by pituitary adenomas that produce ACTH (CD), 15–20 % - by non-pituitary tumors that produce ACTH (ACTH-ectopic syndrome), and < 1 % - by hypothalamic tumors that produce corticotropin-releasing hormone.

Non-pituitary (ectopic) secretion of ACTH most often occurs as a result of small cell carcinoma or carcinoid tumor of the lungs, bronchi, less often – medullary cancer of the thyroid gland, cancer of cells of the islets of Langerhans, pheochromocytoma, gastrinoma, tumor of the gastrointestinal tract, urinary bladder, parotid and salivary glands, as well as thymus carcinoid, appendix, etc.

Although most cases of HCor are not inherited, in rare cases it is the result of an inherited predisposition to develop tumors in one or more of the hormone-secreting glands. Children or young adults with primary pigmented adrenocortical nodules develop small tumors that produce cortisol in the adrenal glands. CS can be presented together with the genetic disorder multiple endocrine neoplasia (MEN) type 1, which is associated with hormone-secreting tumors of the lung, pancreas, parathyroid glands, or pituitary gland.

Endogenous HCor, caused by a tumor of the adrenal glands or pituitary gland, affects women five times more often than men. Symptoms usually manifest between the ages of 25 and 40. At an older age, men suffer from ACTH-ectopic

syndrome 3 times more often than women, which is caused by malignant neoplasms of the lungs and bronchi. ACTH-producing pituitary adenomas in children are usually larger and grow somewhat faster than in adults. The incidence evaluation of HCor morbidity is imprecise and probably underestimates the frequency of iatrogenic CS, mild HC, and ACTH-ectopic syndrome.

2.3. Classification of HC

Depending on the prevailing hormonal secretion, there are 4 main syndromes of HC.

1. CS – hyperproduction of glucocorticoids.
2. Virilization syndrome (adrenogenital syndrome) – hyperproduction of androgens.
3. Feminization syndrome – hyperproduction of estrogens.
4. Hyperaldosteronism – hyperproduction of mineralocorticoids.

The most common combination is a combination of CS with viral syndrome.

Depending on the involvement of all or individual layers of the adrenal cortex, the following two forms of HC are defined:

1) total HC;
2) partial HC.

The total HC includes:

- CD (central, dependent on ACTH, form of HC);
- CS due to corticosteroma (most often malignant) of the adrenal gland (ACTH-independent form of HC);
- CS caused by a tumor producing ACTH-like substances or corticoliberin (ACTH-dependent ectopic HC);
- HC due to the development of autonomous macronodular hyperplasia of the adrenal glands.

Partial HC occurs due to the development of:

- androsteroma (most often malignant) – a virilizing tumor of the cortex of the adrenal glands;
- corticostroma (most often malignant) – a feminizing tumor of the adrenal cortex;
- mixed tumors of the adrenal cortex;
- aldosteromas (primary hyperaldosteronism).

Due to the fact that in most cases of HC there is an increase in the secretion of cortisol with the corresponding development of CS or CD, the terms «HC» and «HCor» are often equated.

Thus, CS and CD are states that combine the concepts of HCor. The main difference between the syndrome and the disease is the localization of the primary lesion:

- in CD – primary damage to the pituitary gland or hypothalamus with excessive production of ACTH or (less often) corticotropin-releasing hormone, which leads to the development of secondary bilateral diffuse hyperplasia of the cortical substance of the adrenal glands with increased cortisol production;
- with CS, HC is due to endogenous hyperproduction of glucocorticoids by the adrenal glands with their primary damage or long-term use of corticosteroid drugs.

Etiopathogenetic classification of HCor

1. Endogenous CS:

1.1. ACTH - dependent CS:

- excessive secretion of ACTH by the pituitary gland (pituitary tumor or hyperplasia of corticotrophs of the adenohypophysis) – pituitary CS (from 68–70 % to 80–85 % of all cases);
- ACTH-producing ectopic tumor: oat cell lung cancer, medullary thyroid cancer, chromaphenoma, ovarian, testicular or prostate cancer; carcinoid of the lungs, bronchi, thymus, pancreas, appendix; tumors of the

gastrointestinal tract, bladder, tumors of parotid and salivary glands, etc. (from 5–10 % to 10–15 %), as well as other tumors that secrete ACTH or similar compounds;

- unknown source of ACTH production (5 %);
- ectopic production of corticoliberin by tumors is less than 1 %.

1.2. ACTH-independent CS (adrenal) – excessive secretion of cortisol by the adrenal glands as a result of their primary damage (10–20 %):

- adrenal gland adenoma – 10 %;
- adenocarcinoma of the adrenal glands – 5 %;
- micronodular adrenal hyperplasia (unilateral or bilateral), sporadic or as part of the Carney syndrome manifestation (combination with lentiginosis, myxomas of the heart and skin, large-cell sertolioma, as well as with a number of other neoplasias) – rarely;
- macronodular adrenal hyperplasia, sporadic, or due to the presence of ectopic receptors for gastric inhibitory peptide, lutropin, choriogonadotropin, gastrin-inhibitory polypeptide, vasopressin, immunoglobulins, interleukin-1, β-adrenoceptor agonists - less than 2 %;
- primary pigmented nodular disease of the adrenal glands - less than 2 %;
- nodular hyperplasia as part of the McCune-Albright syndrome (a rare congenital developmental disorder that manifests itself in childhood or early adolescence and combines polyostotic fibrous dysplasia of the bone, skin pigmentation like «coffee with milk» and endocrine pathology) - rarely;
- subclinical CS is an «incomplete» syndrome of HC, which is observed in formations of the adrenal glands.

2. Exogenous CS (iatrogenic) – develops later in patients who receive glucocorticoids for certain diseases (including bronchial asthma, rheumatoid arthritis, systemic lupus erythematosus, skin diseases, etc.).

3. Functional HCor (pseudo-Cushing's) in the presence of neuro-metabolic-endocrine syndrome, obesity, diabetes mellitus, puberty-adolescent dyspituitarism, alcoholism, liver diseases.
4. Physiological HCor under conditions of pregnancy.
5. CS with a cyclic course (hypercortisolemia alternates with periods of normal hormone levels); in this case, the external signs of CS may appear against the background of normocortisolemia.
6. «Silent» corticotropinoma - the tumor produces biologically inactive ACTH, which is not accompanied by an increase in the cortisol level and the appearance of CS signs.

2.4. Clinical variants of HC, laboratory-instrumental diagnostics and methods of treatment

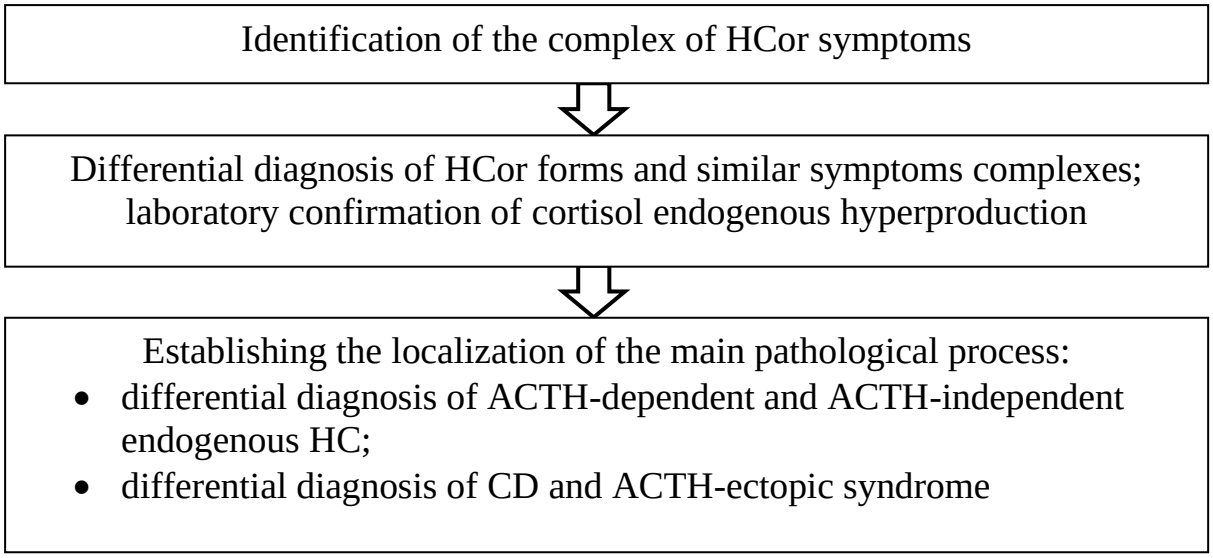
The clinical picture of HC depends on which hormone hyperproduction occurs in the patient (Table 1).

Table 1

Symptoms caused by excessive secretion of glucocorticosteroids	– a moon-shaped face with a crimson-cyanotic color; - trophic skin changes; - acne; - purplish-cyanotic stretch marks on the chest, in the area of the mammary glands, on the abdomen, in the area of the shoulders, on the inner surface of the thighs; – dysplastic obesity with fat deposition on the face, neck, chest, abdomen and thinning of the limbs; - the development of muscle hypotrophy and atrophy, which is manifested by obliqueness of the buttocks, muscle weakness, impaired motor activity, proximal myopathy, as well as the risk of the appearance of various localization hernias; - osteoporosis and osteopenia, which can be accompanied by pathological fractures and compression of the vertebral bodies with a decrease in height; – nephrolithiasis and inflammatory changes in the kidneys; - opportunistic and fungal infections due to secondary immunodeficiency; – impairment of carbohydrate metabolism (glucose intolerance or development of secondary (steroid) diabetes); – encephalopathy, mental disorders
Symptoms caused by excessive secretion of mineralocorticoids	-arterial hypertension resistant to antihypertensive therapy; – myopathies and dyshormonal myocardiodystrophy with the development of heart rhythm disorders and progressive heart failure; – imbalance of electrolytes, in particular potassium and sodium; - fluid retention in the body (edema)
Symptoms caused by excessive secretion of sex hormones	- in women - signs of androgenization: hirsutism, hypertrichosis, menstrual cycle disorders and impaired fertility; - in men with the development of estrogen-producing tumors: change in the tone of voice, intensity of beard and mustache growth, gynecomastia, decreased potency and impaired fertility

2.4.1. HC with predominant secretion of glucocorticoids - HCor - features of the clinical course, diagnosis and treatment

The diagnostic stages for HCor are as follows:



Clinical and anamnestic criteria for the HCor diagnosis

It is known that HCor causes the development of various complications and significantly increases the risk of mortality. Thus, timely detection and diagnosis as well as adequate therapy of the specified pathology will be accompanied by the avoidance of possible adverse consequences.

Groups of patients who should be screened for the probable presence of HCor:

- patients with changes in appearance and other multiple clinical manifestations that progress and are inherent in HCor, namely: dysplastic obesity with thin hypotrophic limbs, matronism (bright blush on the cheeks), bright wide > 1 cm striae (anterior abdominal wall, thighs, axillary areas, etc.), petechiae and ecchymoses with easy bruising, hirsutism, alopecia, proximal myopathy;

- young people with unusual clinical symptoms for their age, in particular, osteoporosis with low-traumatic fractures, type 2 diabetes mellitus, obesity, arterial hypertension;
- women with the development of secondary amenorrhea and men with a decrease in sexual desire,
- persons with a rapid increase in body weight in combination with pronounced general and muscle weakness;
- children who have growth retardation along with an increase in body weight;
- patients with an incidentally discovered neoplasm of the adrenal glands;
- patients of any age with poorly controlled diabetes mellitus and/or hypertension combined with obesity or rapid weight gain;
- patients with the vertebral bodies fractures, especially multiple fractures, under the age of 65.

When collecting anamnesis, it is advisable to analyze old photographs of the patient to establish possible changes in appearance and determine the approximate duration of the disease, as well as to find out the presence of fractures in the past with minimal trauma, pain in the bones, muscle weakness, convulsions, clarify the state of the menstrual cycle, during questioning to form an idea about the psycho-emotional state of the patient. A history of diabetes mellitus, arterial hypertension, low-traumatic fractures, urolithiasis, often chronic recurrent pyelonephritis, cystitis, sinusitis, and other purulent diseases can also be an indirect sign of HCor. It is mandatory to clarify the patient's use of hormonal drugs, in particular, glucocorticoids, even over-the-counter local creams to rule out the possibility of the development of exogenous HCor.

Preliminary diagnosis of HCor is established on the basis of history and typical clinical signs of the disease.

Laboratory-instrumental diagnostics of HCor

Laboratory-instrumental diagnosis of HCor is difficult. There is no single screening test that reliably confirms or excludes CS/CD. When interpreting the results, the clinical picture and the advantages and disadvantages of individual studies should be taken into account. A positive result of one screening test is not enough to make an accurate diagnosis of HCor, an additional test is needed for confirmation. And vice versa, if there are clinical signs indicating HCor, a negative result of one study is not enough to rule out the pathology. It is always necessary to exclude the patient's previous use of glucocorticoids (exogenous CS) and the presence of factors that can potentially affect the increase in the level of endogenous cortisol with the corresponding development of functional HCor (Table 2).

Table 2

Conditions leading to functional hypercortisolism

Clinical and laboratory changes	A condition or disease
Clinical symptoms of HCor are present, combined with an increase in blood cortisol level	– pregnancy; – depression or other serious psychiatric pathology; – alcoholism; - resistance to glucocorticoids; – morbid obesity; - poorly controlled diabetes mellitus
Clinical symptoms of HCor are usually absent, while an increase in blood cortisol level is determined in the laboratory	– any stress (hospitalization, surgical interventions, pain, etc.); - severe malabsorption, malnutrition, anorexia nervosa; – exhausting training; – hypothalamic amenorrhea; – an increase in the level of cortisol-binding globulin (increased cortisol level in the blood, but not in the urine)

Hormonal studies

- ACTH: the secretion of the hormone into the blood is characterized by daily rhythms, the concentration is maximum from 7.00 to 8.00 in the morning, and the minimum – around 11.00–24.00;
- cortisol in blood serum: normally the level is maximum at 8:00 a.m., at 11:00 p.m.–10:00 p.m. – minimum; the difference between morning and evening concentration > 100 nmol/l;
- free cortisol in daily urine is the main diagnostic test for adrenal cortex dysfunction, the method has high sensitivity and specificity;
- cortisol in saliva – a test for the detection of HC, reflects the concentration of free (not bound to proteins) cortisol, and even excludes the effect of the circadian rhythm of cortisol; the cortisol content in saliva does not depend on its volume;
- 17-oxycorticosteroids (17-OCS) in urine – excretion of glucocorticoid hormones and their metabolites with urine.

NB! Changes in blood and saliva cortisol concentration are unidirectional as against the background of a normal circadian secretion rhythm (peak at 7.00–9.00, minimum level – at midnight), and against its background disorders (endogenous HC, hypocorticism). Study of cortisol in saliva has advantages over a blood test: saliva contains free cortisol, the level of which does not depend on the content of cortisone-binding globulin; biomaterial is stable, material collection is comfortable for the patient: it is painless, non-invasive, inexpensive in terms of times, does not require the participation of medical staff, hospitalization, pharmacological impact. Saliva collection is carried out only at night: 23:00–24:00 and necessarily twice – on different days.

Evidential confirmation of HCor are the following laboratory indicators:

- increase in daily excretion of free cortisol with urine over 100 μg per day;

- an increase in the blood cortisol level more than 23 μg/dL or 650 nmol/l during a 2-fold study (it is necessary to exclude the influence of certain side factors on the cortisol level);
- shifts in the concentration of ACTH in the blood (significant increase - in case of ACTH-ectopy (more than 2.5-3.0 times), CD (> 20 pg/ml) or decrease (< 10 pg/ml) - in case of adrenal genesis of CS) .

Indirect laboratory signs of HCor are:

• hyperglycemia or impaired glucose tolerance;

• hypernatremia and hypokalemia;

• neutrophilic leukocytosis and erythrocytosis;

• calciuria;

• alkaline reaction of urine;

• increase in urea level.

In doubtful cases, functional tests are carried out:

- determining the daily rhythm based on the level of cortisol and ACTH in the blood plasma (normally, the cortisol level begins to rise from 03:00 to 04:00, reaching a peak at 07:00 to 09:00, decreases until the end of the day with a minimum indicator in a calm state and in sleep); with CD/CS, the circadian rhythm is impaired);
- dexamethasone suppression tests (Liddle's large and small tests).

*1) Small suppression test with dexamethasone.*The test is based on the inhibition of endogenous ACTH production by high concentrations of exogenous glucocorticosteroids based on the principle of negative feedback. A small test is carried out for the differential diagnosis of pathological endogenous and functional HCor.

The test has two options

Option No. 1. Determination of daily excretion of urine cortisol. For 2 days, every 6 hours of taking 0.5 mg of dexamethasone (total dose of 4 mg). On the second day of taking the drug, collect daily urine for cortisol.

Option No. 2. Determination of blood cortisol (8.00 or 9.00). Taking 1 mg of dexamethasone every 24 hours. Determination of cortisol in the blood (8.00 or 9.00) the next day.

Interpretation of results. In persons suffering from CD or CS, during a small test, no changes in the secretion of corticosteroids are noted.

*2) Large test with dexamethasone.*A large test is carried out for the differential diagnosis of CD (ACTH-dependent HCor) and CS (ACTH-independent HCor). Doses of dexamethasone used in this test inhibit ACTH secretion in a negative feedback manner and, accordingly, cortisol secretion if HCor is ACTH-dependent.

The test also has two options.

Option No. 1. Determination of daily excretion of urine cortisol. For 2 days, every 6 hours, 2 mg of dexamethasone (total dose of 16 mg) is taken. On the 2nd day of taking the drug, daily urine collection for cortisol.

Option No. 2. Determination of blood cortisol (8.00). Taking 8 mg of dexamethasone every 24 hours. Determination of cortisol in the blood (8.00) on the next day.

Interpretation of results.A decrease in the level of cortisol by 50% or more from the initial level is determined with CD. In ACTH-independent forms of CS, the specified decrease in the level of cortisol does not occur, because the production of hormones by the tumor does not depend on hypothalamic-pituitary connections.

Schematically, the algorithm for interpreting the level of ACTH under the conditions of HCor clinical and biochemical evidence is shown in fig. 1.

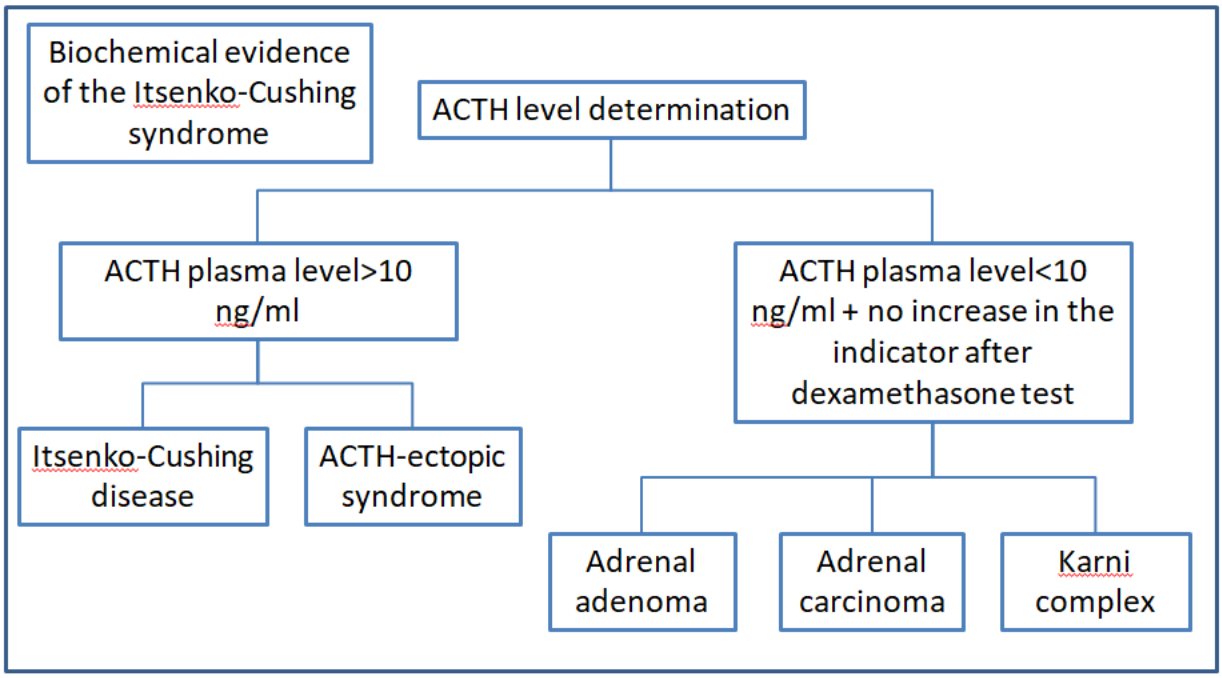


Fig. 1. Algorithm for HCor diagnosing

Topical diagnosis includes:

- ultrasound examination (US) of the adrenal glands (the informativeness of the method is 60–80 %).

NB! Ultrasound does not allow to evaluate the size of the adrenal glands and is therefore not a recommended method for imaging the adrenal glands;

- MRI or CT of the adrenal glands (informativeness of the method is 90–95 %);
- scintigraphy of the adrenal glands with ^{131}I-cholesterol (the method allows you to assess the functional activity of the adrenal glands; asymmetric accumulation of the isotope can serve as a guide for surgical intervention - it is increased on the side of the tumor);
- X-ray of the skull;
- MRI or CT with contrast of the brain.

To detect the localization of ACTH or corticoliberin production in ACTH-ectopic syndrome, an examination is recommended, which is aimed at finding a tumor and should include imaging of the lungs, thyroid gland, pancreas, thymus, and gastrointestinal tract.

Schematically, the diagnosis and differential diagnosis of various forms of HCor can be presented as follows:

Stage 1. Detection of HC and differential diagnosis with functional HC (obesity, metabolic syndrome, pubertal-juvenile dyspituitarism):
- anamnesis collection;
– clinical examination;
– determination of the daily rhythm of cortisol secretion in blood plasma (at 8:00 a.m. and 11:00 p.m.);
– determination of daily urinary excretion of free cortisol;
– a small test with dexamethasone.

⇩

Results of the 1st stage of the examination

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Pathologic(CS, CD, ACTH-ectopic syndrome, macro- or micronodular hyperplasia):
- the level of cortisol in the blood is increased and its rhythm is disturbed;
- daily excretion of cortisol is increased;
- a small test with dexamethasone is negative.

Functional:
- the cortisol level is normal or slightly increased, but the rhythm is not disturbed;
- daily excretion of cortisol is normal or slightly increased;
- a small test with dexamethasone is positive.

Stage 2. Differential diagnosis of pathological HCor:
- determination of ACTH secretion rhythm in blood plasma (at 8:00 a.m. and 11:00 p.m.);
- an alternative approach is catheterization of both stony veins (which drain from the pituitary gland) and determination of ACTH in the blood from these veins in order to clarify the localization of the source of ACTH;

⇩

Results of the 2nd stage of the examination

Parameter	CD	ACTH-ectopy	CS	Macro- or micro-nodular dysplasia
Cortisol, rhythm	increased, impaired	increased, impaired	increased, impaired	incresed, impaired
ACTH, rhythm	increased, impaired	increased, impaired	reduced, impaired	reduced, impaired
Cortisol in urine	increased	increased	increased	increased
A large test with dexamethasone	positive	positive/ negative	negative	negative

Stage 3: Topical diagnosis of the pathological process:
- X-ray of the skull;
– MRI or CT with contrast of the brain;
– US of the adrenal glands;
– CT scan or MRI of the adrenal glands.

Results of the 3rd stage of the examination

Diagnosis	X-ray of the skull	MRI or CT with contrast of the brain	CT or MRI of the adrenal glands	US of the adrenal glands
CD	osteoporosis of the back, "double contour" of the bottom, enlargement of the Turkish saddle	pituitary tumor or its hyperplasia	bilateral hyperplasia	bilateral hyperplasia
CS	no pathology	no pathology	a neoplasm of one adrenal gland and signs of atrophy of the other	a neoplasm of one adrenal gland
Macro- or micro-nodular dysplasia	no pathology	no pathology	bilateral hyperplasia	bilateral hyperplasia

Additional diagnostic methods include:

- ophthalmologic examination: narrowing of the field of vision (bitemporal hemianopsia) - with macroadenomas of the pituitary gland;
- ECG with detection of myocardial dystrophy signs;
- bone densitometry to assess the presence of osteoporosis or osteopenia;
- gynecologic examination to evaluate the state of the uterus and ovaries;
- fibrogastroduodenoscopy.

Assessment of the HCor severity degree:

– *light form* is characterized by a combination of 3–4 HC signs (more often dysplastic obesity, trophic skin changes, moderate hypertension, sexual dysfunction and mild osteoporosis);

– *medium severity*: there are almost all manifestations of HC, but there are no complications;

– *severe form*: severe HC syndrome with complications: heart failure, stroke, severe osteoporosis with multiple compression fractures of the vertebral bodies, rib fractures, infectious and inflammatory complications with the possible development of sepsis,

Treatment of HCor (CS and CD).

The goal of treatment of all HCor forms is to achieve remission of the disease. Complete remission is considered the disappearance of clinical and hormonal signs of HC. At the same time, the basal blood cortisol level should not exceed 2 mg/dL (50 mmol/l), free urine cortisol should be lower than 20 ng/day (55 mmol/day).

Treatment of ACTH-dependent HCor (CD and ACTH-ectopic CS)

The main factors determining the choice of treatment method include:

- age of the patient;
- size (macro- or microadenoma) and features of growth of pituitary adenoma (corticotropinoma);
- disease severity;
- the presence of concomitant pathology and its severity;
- the patient's wishes.

Removal of the tumor that led to the development of HC is considered optimal. If the tumor cannot be radically removed for one reason or another, other methods of normalizing blood cortisol are considered.

AND. Surgical treatment of CD

Surgical transsphenoidal removal of corticotropinoma

Pituitary adenomas that produce an excessive amount of ACTH are subject to surgical removal (transsphenoidal adenomectomy, transcranial adenomectomy) (Fig. 2).

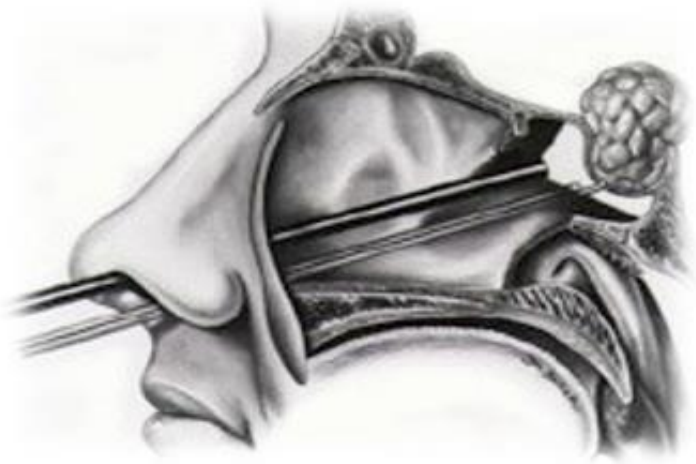

Fig. 2. Transsphenoidal removal of corticotropinoma

With radical removal, the effect occurs in 7–10 days. The method can be used alone or in combination with adrenalectomy and/or radiotherapy.

Possible complications of neurosurgical interventions:

- hemorrhage in the cavernous sinus or its damage;
- nasal liquor;
- meningitis;
- sinusitis;
- hypopituitary syndrome (partial or complete).

NB! In the presence of a microadenoma, the efficiency of the surgical treatment is 90 %, but if the size of the adenoma is very large (macroadenoma) - only 65 %.

B. Radiotherapy (radiation therapy) of CD

There are three methods of radiotherapy:

1. Gamma therapy (γ-therapy).

2. Stereotaxic radiosurgery (at a dose of 70–90 Gy).
3. Proton irradiation:

a) as an independent method (in case of light and medium-severe course);

b) in combination with adrenalectomy (in case of moderate and severe course).

Proton therapy for the pituitary region is primarily used in the treatment (possibly with unilateral adrenalectomy):

– patients under 20 years of age;

– patients who refused neurosurgical intervention;

- patients who have contraindications to neurosurgical intervention;

- with proven CD, but without clear signs of pituitary adenoma.

The effect comes in 4–6 months. In the case of combined treatment, adrenalectomy should be performed as the first stage, because it contributes to shortening the period of onset of remission. A possible side effect of radiation therapy is the hypopituitary syndrome (both loss of certain tropic functions and panhypopituitarism).

S. Drug therapy of CD

Drug therapy (blockers of steroidogenesis) is an auxiliary method of treatment used in preparation for surgery or radiation therapy.

Medicines used for the treatment of CD are divided according to the mechanism of action:

1) steroidogenesis blockers: aminoglutethimide derivatives (Mamomit, Orimeten), β-hydroxylase inhibitors (Metyrapon), parachlorophenyl derivatives (Chloditan, Mitotane), ketoconazole derivatives (Nizoral);

2) glucocorticoid receptor blockers (Mifepristone).

Their disadvantage is the ability to control only the symptoms of the disease (due to blocking the effects of hormones), and not the levels of cortisol and ACTH;

3) pituitary-targeted therapy - involves the use of drugs that can suppress the production of ACTH, thus normalizing the level of cortisol in the blood. Dopamine receptor agonists (Cabergoline) and somatostatin analog Pasireotide (Signifor, Signifor LAR) are among such agents.

– Cabergoline is prescribed 1–2 times a week in a dose of 0.5 to 3 mg; there are data that its effectiveness increases when used in combination with ketoconazole.

– Signifor is produced in the form of a solution for injections of 0.3 mg/ml, 0.6 mg/ml, 0.9 mg/ml. The recommended starting dose is 0.6 mg twice a day subcutaneously. If there is no response to the treatment 2 months after the start of therapy, it should not be continued.

– Signifor LAR (passireotide with extended release) is produced in the form of a powder for preparing a suspension of 20 and 40 mg in a vial. Treatment begins with 10 mg (maximum dose – 40 mg) intramuscularly deep once every 28 days. The dose should be titrated every 2–4 months (depending on the effect of treatment and tolerability).

Clinical experience shows that pasireotide, mifepristone, cabergoline in monotherapy have a temporary effect. The most promising is combined treatment:

- pasioretide monotherapy provides 29 % efficiency;
- pasireotide + cabergoline – 53 %;
- pasireotide + cabergoline + ketoconazole – 88 %, which is comparable in effectiveness to neurosurgery. Pacioretide and cabergoline block the production of ACTH by the adenoma, and ketoconazole inhibits steroidogenesis.

In addition, the last combination of drugs makes it possible to reduce the dose of each of them, which means fewer side effects described in the instructions for these drugs.

The duration of conservative therapy depends on the purpose of the administration (as an independent method or a preparatory stage of therapy), clinical features of the course of the disease, tolerability of treatment.

Treatment of an ectopic ACTH- or corticoliberin-synthesizing tumor

Treatment of ACTH-ectopic syndrome consists in the removal of an extrapituitary tumor that produces ACTH and is carried out depending on the location and stage of the primary tumor, taking into account the severity of HC. Can be used alone or in combination with adrenalectomy and/or radiotherapy. In cases where the tumor is disseminated and cannot be removed, steroidogenesis inhibitors are used.

Adrenalectomy

It can be unilateral or bilateral. It is used in the following cases:

– in combination with radiotherapy of the primary tumor area;

– in case of ineffective removal of an ACTH-secreting tumor;

– bilateral adrenalectomy as the first stage of treatment in severe progressive HC followed by radiation therapy to prevent Nelson's syndrome.

The effect comes in 4–6 months.

Bilateral adrenalectomy has been used less frequently in recent years, but the absolute indication for its performance is the severe course of the disease and the impossibility of compensating the condition with other available methods. This is due to the fact that the use of bilateral adrenalectomy leads to the emergence of chronic adrenal insufficiency in the patient, and this pathology requires lifelong replacement therapy with glucocorticoids and mineralocorticoids. Bilateral adrenalectomy can also be complicated (in 10–50 %) by Nelson's syndrome – a combination of primary chronic adrenal insufficiency (after surgical treatment or long-term use of chloditan) with progressive pituitary corticotropinoma.

In recent years, the method of destruction of the adrenal glands has been used, which involves the destruction of the hyperplastic substance of the adrenal gland by injecting sclerosing substances under the control of US or CT (selective phlebography). As a sclerosing substance, a mixture of 96 % ethanol solution and 76 % urographin solution in a ratio of 3:1 is usually used. The amount of fluid

injected is determined by the degree of hyperplasia of the adrenal gland and its volume. As a rule, the destruction of the adrenal glands is not used as an independent method of treatment (usually in combination with radiation therapy or adenomectomy).

Treatment of ACTH-independent HCor

The method of choice is surgical treatment. When a volumetric tumor of the adrenal gland with hormonal activity is detected, surgical intervention is indicated, taking into account the size of the tumor and its relationship with the organs and tissues surrounding it. Inhibitors of steroidogenesis are used as preoperative preparation (see above), hypertension, diabetes mellitus, concomitant infectious diseases (most often pyelonephritis), and osteoporosis should also be treated. In cases of adrenal insufficiency after adrenalectomy, corticosteroid replacement therapy is prescribed.

In the presence of **an autonomous tumor of the adrenal cortex** (adenoma), its surgical removal (more often unilateral adrenalectomy) is recommended after preoperative preparation. In the postoperative period, as a result of inhibition of ACTH secretion by previous hypercortisolemia, symptoms of hypocortisolism may occur, which will require temporary replacement therapy with hydrocortisone. In the future, when the function of the remaining adrenal gland is restored, the dose of replacement therapy can be reduced or canceled.

With **macro- or micronodular hyperplasia of the adrenal glands** as the cause of HCor, removal of both adrenal glands is considered the method of choice. The consequence of bilateral adrenalectomy is the development of chronic adrenal insufficiency, which requires constant hormone replacement therapy.

With **cancer of the adrenal cortex** an adrenalectomy of the affected adrenal gland is performed, followed by the appointment (if necessary) of hormone replacement therapy. The need to use additional treatment methods is decided by oncologists in each case individually.

In the case of the impossibility of surgical treatment due to, for example, advanced age, the patient's serious condition, or his disagreement regarding surgical intervention, treatment can be carried out with the help of steroidogenesis blockers or glucocorticoid receptor blockers (see above).

With iatrogenic HCor, it is necessary to minimize the dose of glucocorticosteroids or completely cancel them. At the same time, it is advisable to prescribe symptomatic therapy aimed at eliminating existing disorders. Symptomatic therapy involves the administration of hypotensive agents, potassium and spironolactone preparations, hypoglycemic therapy, and drugs that increase the strength of bone tissue.

2.4.2. HC with predominant secretion of mineralocorticoids – hyperaldosteronism (HA) - features of the clinical course, diagnosis and treatment

Mineralocorticoids, mainly aldosterone, are synthesized only in the glomerular zone of the adrenal cortex (15 % of the thickness of the cortex). The stimulator of aldosterone production is angiotensin II and, to a lesser extent, ACTH.

Primary and secondary HA are distinguished.

Primary HA (PHA), or Conn's syndrome, is a disease caused by excessive production of aldosterone by a hormonally active tumor of the glomerular zone of the adrenal cortex (aldosteroma), much less often by bilateral hyperplasia of the glomerular zone. The disease is relatively rare, it occurs more often in women aged 20–50 years.

The biosynthesis of aldosterone in the tumor is increased 40–100 times, cortisol – 2–5 times, and corticosterone – 2–4 times. An increase in the biosynthesis of cortisol and corticosterone in the tumor is associated with the heterogeneity of the adenoma structure, which in some cases has cells similar to the cells of the bundle zone, and in others – cells that resemble cells of the reticular

zone. However, with primary aldosteronism, not only the glomerular, but also the reticular zone is enlarged.

Secondary HA– a clinical syndrome caused by increased secretion of aldosterone by normal adrenal glands in response to a change in the electrolyte composition of the blood, and sometimes caused by insufficient inactivation of aldosterone in the liver. The cause of secondary HA can be diseases accompanied by acute renal ischemia (hypertensive disease, renal hypertension). Secondary HA can occur in heart failure, edematous forms of kidney pathology (nephrotic syndrome, acute diffuse glomerulonephritis), liver diseases, as well as in diseases accompanied by polyuria or natriuria (decompensated diabetes insipidus and diabetes mellitus, nephritis with sodium loss, etc.). The causes of secondary HA can be myocardial infarction, pneumonia, long-term therapy with diuretics that have natriuretic properties, prolonged stay on a diet with low sodium chloride content etc.

Clinical manifestations of HA are shown in Table 3.

Table 3

Clinical manifestations of primary and secondary HA

HA form	Clinical manifestations
PHA	1) symptoms associated with arterial hypertension (headache, changes in the fundus, heart hypertrophy); 2) neuromuscular symptoms (tetany, muscle weakness, paresthesias and convulsions); 3) renal symptoms (polyuria, polydipsia, nocturia, moderate proteinuria, alkaline reaction of urine)
Secondary HA	depend on the underlying disease, most often, secondary HA is manifested by an edematous syndrome.

Laboratory-instrumental diagnosis of HA

- Concentration of potassium in the blood. Depending on the severity of hypokalemia, it is proposed to distinguish three main subgroups of patients:

1 – with persistent hypokalemia,

2 – with intermittent, transient hypokalemia, which is revealed during repeated examinations,

3 – with normokalemia, which is more often determined in the initial stages of the disease.

Sometimes hypokalemia in Conn's syndrome becomes obvious when an intercurrent disease is added, for example, after a gastroenteritis. In the patient's body with PHA, there is a decrease in the content of total metabolizable potassium, in some cases, hypokalemia is combined with hyperkalemia. Hypokalemia can cause characteristic disturbances on the ECG with changes in the magnitude and direction of the T and U waves, the ST segment, prolongation of the QT interval, and provoke heart rhythm disturbances (most often ventricular extrasystole). These changes may increase against the background of taking diuretics, indications of intolerance to which (increased muscle weakness, convulsions) often occur in the anamnesis of patients with PHA.

- The level of sodium in the blood is elevated, but only a tendency to hypernatremia can be established.
- An increase in blood pH (from 7.46 to 7.60) is hypochloremic alkalosis.
- Glycemia. The level of glucose in the blood is usually normal, but in some patients with Conn's syndrome, moderate hyperglycemia is detected, often impairment of glucose tolerance are established in the dynamics of stress tests.
- Increase in daily diuresis to 2–7 L, hypoisostenuria, alkaline reaction of urine. Hyperkaliuria and hyponatriuria are also noted, in 50–70 % of patients – moderate proteinuria due to the development of kalipenic tubulopathy.
- Blood renin - the level is significantly reduced.
- Aldosterone - the level is significantly increased.

- The aldosterone-renin ratio is significantly higher than normal. PHA is characterized by a decrease in the level of renin in the patient's blood plasma, and this figure does not rise above certain values when diuretics are administered or with a transition to a vertical position, which usually occurs normally. The criterion for PHA is a combination of low renin activity and high aldosterone concentration, which is determined by the ratio of aldosterone activity to plasma renin activity.
- Imaging methods – CT and MRI of the adrenal glands (see above). However, the very fact of detecting a neoplasm in the adrenal gland does not allow us to evaluate its hormonal activity. Conducting a selective phlebography of the adrenal glands with vein catheterization and determining the aldosterone concentration in the blood flowing from the right and left adrenal gland allows to clarify the diagnosis of aldosteroma.
- Radioisotope study of adrenal glands. To detect aldosteroma, radioisotope imaging of the adrenal glands using 19-iodocholesterol labeled with ^{131}I (photoscintigraphy) is very informative. The latter allows to establish the topography of the adrenal glands, their size and functional activity. Usually, radioisotope imaging of the adrenal glands is performed 7–8 days after intravenous administration of 1–1.5 mCi of the radiopharmaceutical.

Diagnostic tests for PHA.

1. In case of hypokalemia, a test with the aldactone (spironolactone) administration is used, based on the ability of aldactone to block the action of aldosterone on the renal tubules. An increase in the blood potassium level (after internal administration of spironolactone (aldactone) at 100 mg 4 times a day for 3 days) on the morning of the 4th day by more than 1 mmol/l indicates the dependence of hypokalemia on excess aldosterone.
2. Test with hypothiazide load. After a single intake of 100 mg of hypothiazide in patients with PHA, a decrease in the blood potassium level may occur.

The diagnosis algorithm of HA syndrome is shown in fig. 3.

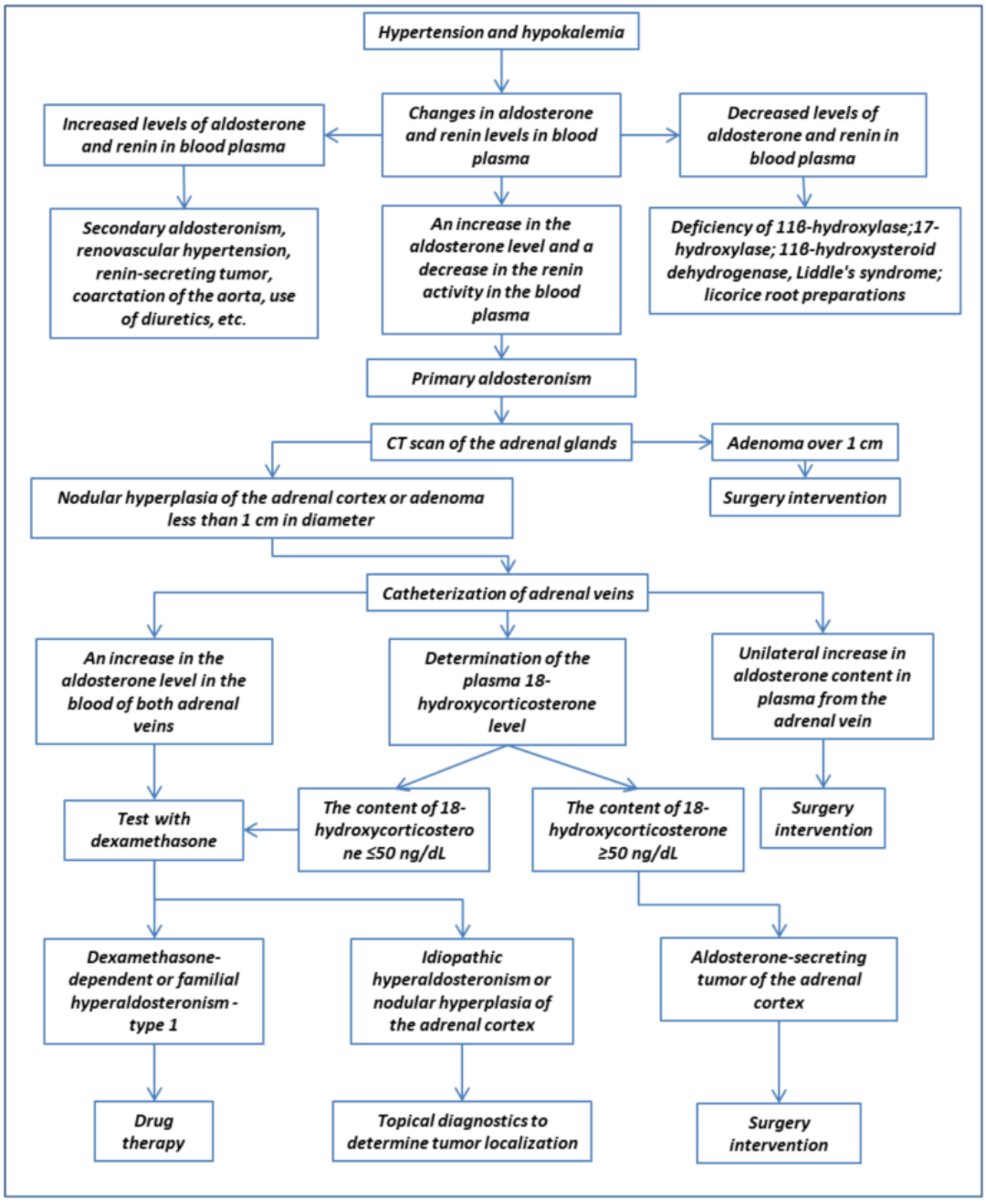

Fig. 3. Diagnostic algorithm for HA syndrome

Treatment of PHA

A radical method of treating PHA is surgical removal of aldosteroma or subtotal/total resection of the adrenal glands in case of their hyperplasia. With PHA, which developed as a result of the adrenal glands hyperplasia, long-term therapy with spironolactone is carried out, and only if it is ineffective - surgical treatment (unilateral total adrenalectomy and resection of 7/8 of the other adrenal

gland volume). In the preoperative period, a diet with a restriction of sodium content and an increase in potassium content is prescribed. In order to normalize the level of potassium in the blood, 0.5 g of potassium chloride 2–3 times a day, 0.025–0.05 g of spironolactone (aldactone or verospiron) 4 times a day are prescribed internally for 7–10 days before the surgery. To avoid acute adrenal cortex insufficiency before surgery and during surgery, glucocorticoids are administered intramuscularly (cortisone, hydrocortisone). In the postoperative period, hormone replacement therapy is prescribed.

Treatment of secondary HA

The main thing is to treat the primary disease and eliminate the factors that contribute to the increased secretion of aldosterone. In case of secondary HA with edematous syndrome, aldosterone antagonists – spironolactone (aldactone, verospiron) are used along with usual diuretics.

2.4.3. HC with predominant hyperproduction of estrogens (feminization syndrome), features of the clinical course, diagnosis and treatment

Hyperproduction of estrogens with the development of feminization syndrome is usually caused by a tumor of the adrenal cortex – corticoestroma. This neoplasm is rare, mostly in men and children of both sexes. In adult women, it is detected accidentally, since it is impossible to detect feminization of women clinically. In women, corticoestroma is diagnosed in the case of its combination with signs of CS.

Features of the clinical course

Clinical manifestations are characterized by the development of feminization elements of men, namely:

– gynecomastia,

– body changes with redistribution of subcutaneous fat according to the female type,

- cessation of beard and mustache growth,

- testicular atrophy, impotence, oligospermia, although the size of the penis and prostate remain normal,

- sometimesAH, weight gain, increased fatigue, depression.

Corticoestroma is usually large and easily palpable, sometimes combined with other tumors of the adrenal cortex.

In some cases, with corticoestroma, symptoms characteristic of CS develop, which is due to hyperproduction of glucocorticoids by the tumor.

Laboratory and instrumental diagnostics.

There is an increased urinary excretion of estrogens, and in some cases 17-ketosteroids (17-KS) and glucocorticoid metabolites (17-OCS).

Methods of visualization and detection of HCor markers - see above.

The data of radioisotope and X-ray diagnostics of the adrenal glands as well as high excretion of estrogens in the urine are of primary importance in the diagnosis of corticoestroma.

Treatment- only surgery (removal of adrenal gland tumor).

2.4.4. HC with predominant hyperproduction of androgens (virilization syndrome or adrenogenital syndrome)

The main adrenal androgens synthesized in the reticular zone of the adrenal cortex are:

- dehydroepiandrosterone (DEA);
- dehydroepiandrosterone sulfate (DEA-s);
- androstenedione

All these substances are weak androgens, but in peripheral tissues they can be transformed into a strong androgen - testosterone. In an adult man, the contribution of adrenal androgens to the total androgen pool is negligible compared to testicular testosterone. In women, on the contrary, the cortex of the adrenal glands is the main source of androgens.

Androsteroma usually leads to the development of HC with predominant hyperproduction of androgens. This tumor secretes large amounts of androgens - DEA and DEA-s, which are markers of adrenal androgens, as well as androstenedione, 11-hydroxy-androstenedione, and testosterone, which determines the clinical picture. The disease can occur at any age in persons of both sexes. Women are diagnosed with tumors twice as often as men. More than half of all virilizing tumors of the adrenal cortex in adults are benign in nature. However, they can be malignant, especially in children. Malignant androsteromas usually metastasize quite late and have a favorable course, but even after removal they can recur. There are cases of germination of the capsule of a malignant tumor and its spread to the kidney tissue. Malignant androsteroma metastasizes to the lungs, liver and kidneys.

The clinic of androsteroma is similar in many respects to congenital dysfunction of the adrenal cortex, but it differs by the rapid development of virilization, which is especially quick in the case of malignant androsteroma. The first clinical sign of an androgen-producing tumor of the adrenal glands is impairment of sexual function, and then the phenomena of masculinization and defeminization are added. Viral syndrome is most clearly manifested in women in the form of hypoplasia of the mammary glands, changes in the tone of voice, the appearance of acne on the skin, hair loss on the head, hypertrophy of the clitoris. At the same time, there are amenorrhea, infertility and often AH. In children, the clinic is accompanied by the syndrome of false precocious puberty of the isosexual type in boys and heterosexual type in girls. Sometimes the clinic of androsteroma is combined with the phenomena of HC according to the type of CS, which is due to hyperproduction of glucocorticoids by the tumor.

Diagnostics has several stages (Fig. 4) and is based on determining:

- high levels of androgens in the blood;

- level 17-KS in daily urine, the number of which increases 10–100 times with androsterom (at the same time, the level of 17-OCS may remain normal or slightly increase).

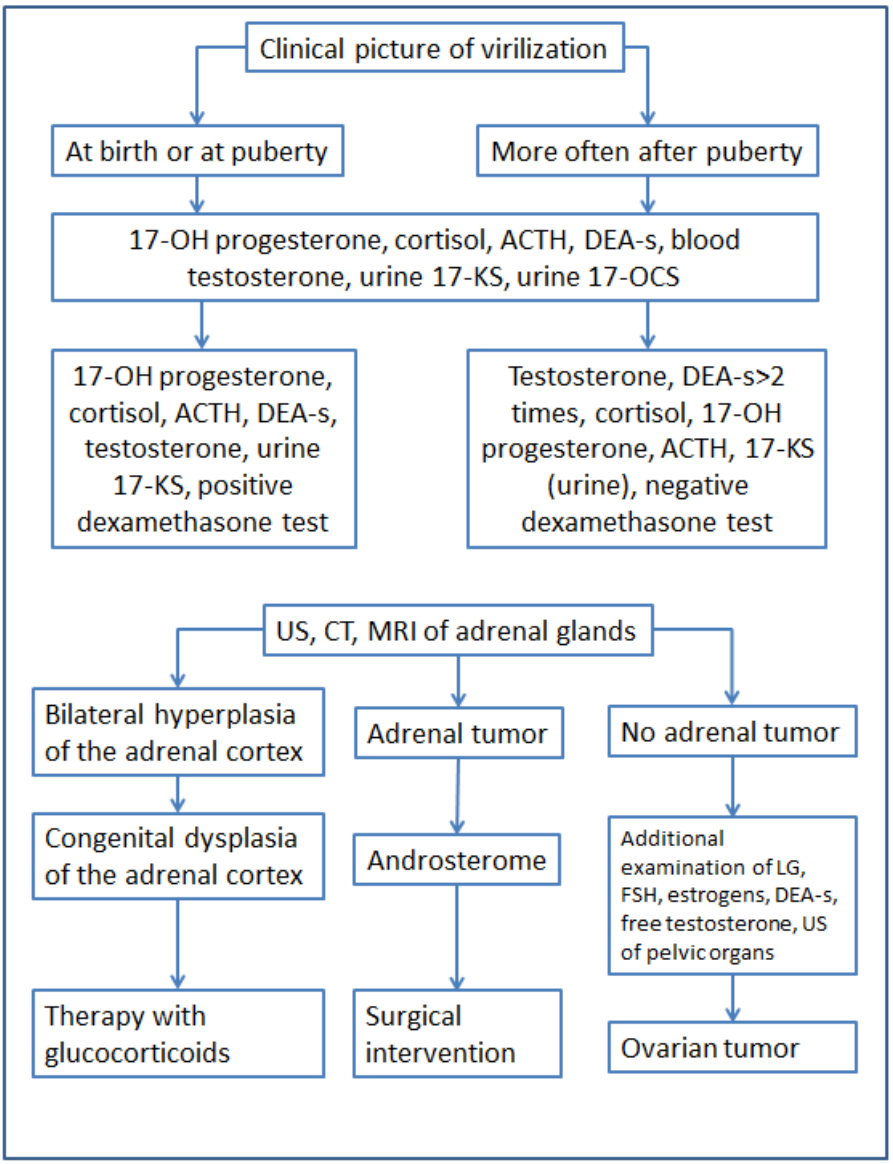

Fig. 4. Algorithm of diagnosis and differential diagnosis of androsteroma

Imaging methods: radioisotope examination of the adrenal glands, X-ray diagnostics (a unilateral tumor of the adrenal gland is detected).

Treatment is only surgery intervention- removal of the adrenal gland affected by the tumor.

TEST QUESTIONS ON THE SUBJECT OF THE LESSON:

1. The cause of Cushing's disease is:
    a) prolactinoma,
    b) ovarian tumor,
    c) corticosteroma,
    d) basophilic pituitary adenoma,
    e) thyrotropinoma.
2. Aldosterone secretion in Conn's syndrome is:
    a) significantly increased,
    b) slightly increased,
    c) not changed,
    d) slightly reduced,
    e) significantly reduced.
3. Typical manifestations of increased production of glucocorticoids are:
    a) weight loss,
    b) stretch marks on the skin,
    c) arterial hypotension,
    d) increased moisture of the skin,
    e) decreased blood glucose level.
4. With a severe form of Cushing's disease, the following are noted:
    a) uniform distribution of the subcutaneous fat layer,
    b) pathological bone fractures,
    c) transient arterial hypertension,
    d) increased differentiation and growth of the skeleton,
    e) preserved menstrual cycle.
5. A complication of Cushing's disease is:
    a) hypotension,
    b) hypothermia,
    c) progressive weight loss,
    d) thrombocytopenia,
    e) kidney failure.
6. A negative result of a large test with dexamethasone allows you to exclude:
    a) Cushing's disease,
    b) adrenal cortex adenomatosis,
    c) glucosteroma,
    d) ectopic ACTH syndrome,
    e) corticosteroma.
7. The differential diagnosis of Cushing's disease is carried out with the following diseases:
    a) chronic pyelonephritis,
    b) chronic adrenal insufficiency,
    c) syndrome of exhausted ovaries,

d) chronic alcoholism,
e) hypothyroidism.

8. Indications for adrenalectomy in Cushing's disease are:
a) ineffectiveness of conservative therapy,
b) progressive weight loss,
c) high level of cortisol in the blood,
d) hypokalemic alkalosis,
e) electrolyte-steroid cardiopathy.

9. The most probable etiological factor of Cushing's disease is:
a) pituitary tumor,
b) brain injury,
c) neuroinfection,
d) adrenal tumor,
e) lung tumor.

10. Corticoestroma is a tumor of the cortex of the adrenal glands, which mainly produces:
a) androgens,
b) estrogens,
c) aldosterone,
d) glucocorticoids,
e) adrenaline.

Answers:1. d; 2. a; 3.b; 4.b; 5. e; 6. a; 7. d; 8. a; 9. a; 10. b.

TASKS FOR SELF-CONTROL

1. What examination should be prescribed to a 30-year-old woman with amenorrhea, arterial hypertension, muscle weakness, stretch marks on the abdomen, and weight gain?
   a) determination of renin in the blood;
   b) determination of cortisol in the blood;
   c) US of abdominal organs;
   d) US of the adrenal glands.

2. A 39-year-old patient complains of excess body weight, shortness of breath during physical exertion, changes in appearance, menstrual cycle disorders. Marbling of the skin, bright red stretch marks on the anterior-lateral surface of the abdomen and lumbosacral region, excessive hair growth on the face and trunk, heart rate 90/min, blood pressure 160/90 mm Hg are determined. X-ray of the skull result - an increase in the size of the Turkish saddle and thinning of its walls. What preliminary diagnosis can be established:
   a) metabolic syndrome;
   b) primary alimentary and constitutional obesity;
   c) Cushing's disease;
   d) Cushing's syndrome.

3. Patient K., 42 years old, complains of headache, flickering flies in front of the eyes, constant thirst, profuse urination. From the anamnesis: in the last six months, he began to notice changes in his appearance: his face became rounder, his limbs became thinner, his stomach increased in volume, he was concerned about dryness of the skin, and hair began to fall out on his head. He consulted a neurologist in connection with lower back pain. Recently, he notes an increase in blood pressure to 200/110 mm Hg., takes lisinopril 10 mg 2 times a day without effect. Objectively: height – 161 cm, body weight – 95 kg, body mass index – 36.7 kg/m2. Excessive deposition of subcutaneous fat in the supraclavicular regions, on the chest and abdomen. The skin is dry, marbled, refined. On the stomach - crimson-red wide striae. In the lungs, breathing is vesicular, the borders of the heart are expanded to the left. The tones of the heart are muffled, rhythmic. The heart rate is 88 per minute. Blood pressure – 170/100mm Hg. The abdomen is soft, painless, enlarged due to subcutaneous fat. The liver and spleen are not enlarged. What disease can you think of:
   a) type 2 diabetes mellitus;
   b) hypertensive disease;
   c) primary hyperaldosteronism;
   d) Cushing's syndrome.

4. A 28-year-old woman complains of amenorrhea lasting 6 months, weight gain, increased facial hair growth, and muscle weakness with periodic cramps in the calf muscles. Objectively: height – 172 cm, body weight – 108 kg, body mass

index – 36.5 kg/m2, round face with pronounced hirsutism, several bruises on the legs, supraclavicular fat pads, «buffalo nape», blood pressure – 160 /90 mm Hg. The initial level of cortisol in the plasma, which was measured at 8 o'clock in the morning, was 23 μg/dL (normal < 5 μg/dL), the level of free cortisol in the urine was 230 μg/day (normal 20–100 μg/day), the level of ACTH in plasma at 8 o'clock in the morning – 150 pg/ml (normal 40–100 pg/ml). When conducting a small suppression test with dexamethasone, the plasma cortisol level did not change; however, during a large suppression test, plasma cortisol levels decreased by more than 60% compared to baseline. What is the diagnosis of this patient:

a) Cushing's syndrome;
b) Cushing's disease;
c) iatrogenic hypercorticism;
d) ACTH-ectopic syndrome.

5. A 49-year-old patient notes an increase in blood pressure within the range of 180/120–200/100 mm Hg during the year. Hypotensive therapy is ineffective. Complaints of muscle weakness, dry mouth, polyuria, headache. Blood plasma sodium – 155 mmol/l, potassium – 3.6 mmol/l. What is the most likely cause of hypertension?

a. pheochromocytoma;
b. primary hyperaldosteronism;
c. hypertensive disease;
d. renal hypertension;
e. Cushing's disease.

Keys:1.b; 2. c; 3. d; 4.b; 5. b.

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Електронне навчальне видання комбінованого використання
Можна використовувати в локальному та мережному режимі

Тихонова Тетяна Михайлівна
Горшунська Мар'яна Юріївна
Барабаш Надія Євгенівна
Мартим'янова Лариса Олексіївна

ВЕДЕННЯ ПАЦІЄНТА З СИНДРОМОМ ГІПЕРКОРТИЦИЗМУ (ХВОРОБОЮ/СИНДРОМОМ ІЦЕНКА-КУШИНГА, ГІПЕРКОРТИЦИЗМОМ З ПЕРЕВАЖНОЮ СЕКРЕЦІЄЮ МІНЕРАЛОКОРТИКОЇДІВ, ЕСТРОГЕНІВ, АНДРОГЕНІВ)

Методичні рекомендації для підготовки до практичних занять здобувачів вищої медичної освіти 6-го року навчання з дисципліни «Внутрішня медицина»

(Англ. мовою)

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