UDC 616.43/.45-092:577.175.32-07-08

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PANHYPOPITUITARISM IN ADULTS: MODERN VIEWS AND CASE ANALYSIS

Abstract

The article is devoted to the problem of panhypopituitarism, the diagnosis of which presents certain difficulties in connection with the combined lesion of several peripheral endocrine glands. Modern classification, etiopathogenesis, diagnosis and treatment of the disease are presented. Acquired hypopituitarism in adults develops, as a rule, at the age of 30–60 years, mostly women are affected. Panhypopituitarism is diagnosed when pituitary production of all tropic hormones is affected, which is observed in case of damage to 90 % of the adenohypophysis cells. The variety of clinical signs of the disease is determined by the different effects of pituitary hormones and the degree of their deficiency. The diagnosis is based on a history of etiological factors causing damage to the pituitary gland, and clinical signs of insufficiency of peripheral endocrine organs, which is confirmed by the results of laboratory studies. In hypopituitarism due to, for example, the growth of pituitary adenoma, the clinical picture develops gradually, and the disorder of the secretion of the pituitary tropic hormones usually occurs in the following sequence: growth hormone, gonadotropins, then thyrotropic and adrenocorticotropic hormones, and, the last one, prolactin. Neurosurgery or hemorrhage in the pituitary gland causes a rapid manifestation of the disease, and the severity of the condition is associated mainly with adrenal insufficiency. In the case of surgery for pituitary adenoma, there is a recommendation to determine morning blood cortisol on the 3rd day after the intervention. Conservative treatment is aimed at compensating for hormone deficiency. According to the clinical significance of endocrine disorders, their correction is carried out in the following sequence — first, compensation for adrenal insufficiency, then thyroid, sex glands and growth hormone. In case of damage to the posterior lobe of the pituitary gland with the development of diabetes insipidus, replacement therapy for vasopressin deficiency is also required. The clinical case presented in the article reflects the difficulty of diagnosis and interpreting the data of hormonal analysis in panhypopituitarism. An analysis of the described clinical case shows the importance of understanding the pathogenesis of the disease when conducting a diagnostic search. Adequate replacement therapy can restore normal well-being in patients with hypopituitarism.

Key words: *hypopituitarism, adenohypophysis, hypocorticism, hypothyroidism, hypogonadism*

For citation: Farkhutdinova L. M. PANHYPOPITUITARISM IN ADULTS: MODERN VIEWS AND CASE ANALYSIS. The Russian Archives of Internal Medicine. 2019; 9(2): 152-160. [In Russian]. DOI: 10.20514/2226-6704-2019-9-2-152-160

DOI: 10.20514/2226-6704-2019-9-2-152-160

ACTH — adrenocorticotropic hormone, IGF-1 — insulin-like growth factor, LH — luteinizing hormone, MRI — magnetic resonance imaging, FT4 — free thyroxine, GH — growth hormone, TSH — thyroid-stimulating hormone, USS — ultrasound scanning, FSH — follicle-stimulating hormone

Good judgment comes from experience,
and experience comes from bad judgment.
Hodja Nasreddin

Diagnosis and treatment of hypopituitarism, or pituitary insufficiency, often present challenges. This is due to the combined affection of several endocrine glands, where symptoms and interpretation of the results of hormonal analysis have a number of peculiarities if compared with isolated damage to a particular organ of internal secretion. Insufficient awareness of the problem of hypopituitarism

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is also important. The author hopes that the presented article with information about the diagnosis and treatment of this disease and the analysis of the clinical case will be of help to practitioners.

Hypopituitarism is caused by a decrease in the secretion of tropic hormones of the adenohypophysis, which is manifested by the functional insufficiency of the corresponding peripheral endocrine organs.

Acquired hypopituitarism in adults is observed usually at the age of 30–60 years; mostly women suffer, due to the higher frequency of diseases that cause this pathology.

Etiopathogenesis

The causes of the syndrome of acquired hypopituitarism include tumors of the pituitary gland and the hypothalamic region, vascular pathology (ischemic or hemorrhagic damage to the pituitary, cavernous sinus thrombosis, etc.), empty sella syndrome, brain injuries, neurosurgical interventions, irradiation of the hypothalamic-pituitary region, as also damage of inflammatory, infectious, infiltrative, and toxic genesis.

The condition for the progression of disease is a direct damage to the pituitary gland or weakening of the stimulating effect of the hypothalamus, releasing hormones of which regulate both functional and proliferative activities of the adenohypophysis being subjected to atrophy when hypothalamic control is reduced. Hypopituitarism is observed when 70–75 % of cells of adenohypophysis are destroyed, panhypopituitarism — in case of damage to 90 % of cells.

Classification

Based on the localization of the pathological process. In case of direct damage to the pituitary gland, primary hypopituitarism is diagnosed, while in case of disorder of the regulatory function of hypothalamus, it is diagnosed as secondary.

Depending on the clinical manifestations, the following forms of the disease are distinguished: isolated hypopituitarism (with loss of one tropic function), partial (in case of disorder of two tropic functions or more, but not all), and also panhypopituitarism (with affection of all tropic functions) [3, 5, 6, 10].

Clinical Course

With hypopituitarism caused by, for example, the growth of pituitary adenoma, the clinical picture develops gradually and it can take several years from the beginning of the disease to diagnosis. Disorder of secretion of tropic hormones of the pituitary gland occurs, as a rule, in the following sequence: first, a decrease in production of growth hormone (GH), gonadotropins (luteinizing hormone, LH, and follicle-stimulating hormone, FSH), then thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH) and, last of all, prolactin, occurs. In this regard, the earliest signs of hypopituitarism are sexual disorders, while the partial lesion of the pituitary gland in most cases is characterized by somato- and gonadotropic insufficiency.

Neurosurgical intervention or hemorrhage in the pituitary gland causes rapid manifestation of the disease, often within a few hours, and the severity of the condition is mainly associated with adrenal insufficiency, requiring immediate replacement therapy.

The variety of clinical manifestations of hypopituitarism is determined by various effects of tropic hormones and the degree of their deficiency.

Hypoproduction of GH leads to a decrease in the intensity of metabolic processes. As a result, the amount of visceral fat and blood cholesterol increases, while muscle mass and bone mineral density decreases; the skin becomes dry and thinned. Tendency to apathy, depression, low self-esteem and ability for social adaptation are typical.

In women, gonadotropin deficiency or hypogonadotropic hypogonadism is manifested by menstrual irregularities (oligo-, opsomenorrhea), infertility, atrophic changes in the vaginal mucosa and urogenital disorders up to urinary incontinence, reduction of pubic hair, hypoplasia of mammary glands, and decrease of libido. Deficiency of gonadotropins in men also causes a decrease in sexual function, gonad atrophy, a reduction in hair on the face and body; gynecomastia is possible. In addition, hypoandrogenism in males leads to development of anemia. Regardless of gender, hypogonadism contributes to the formation of osteoporosis and early atherosclerosis, accompanied by a loss of interest in the world and to oneself.

Characteristic symptoms of thyrotropic insufficiency, causing secondary hypothyroidism, are

drowsiness, lethargy, retardation, cold intolerance, reduced intellectual and physical activity, dry and pale skin, puffy tissue, hair loss on the head, a tendency to bradycardia, and constipation.

Signs of a decrease in ACTH production with the development of secondary hypocorticism include general weakness, fatigue, loss of appetite up to nausea and vomiting, weight loss, decreased blood pressure, especially in orthostasis, a tendency to hypoglycemia manifested by intolerance to hunger, attacks of dizziness on an empty stomach; reduced heart rate is also possible. Patients' well-being worsens in the evening, with emotional and physical stress.

It is also necessary to bear in mind that in case of diseases of the pituitary gland there is a possibility of damage of its posterior lobe — the neurohypophysis. Unlike the anterior lobe, the adenohypophysis, the posterior pituitary is not a hormone-producing gland. Hormones of the posterior lobe (vasopressin and oxytocin) are synthesized in the bodies of the hypothalamic neurons, and then transported along axons and accumulate in their terminal extensions, forming the neurohypophysis. Vasopressin, or an antidiuretic hormone, possesses the main clinical importance providing reabsorption of water in the kidney and increasing the peripheral vascular tone. Deficiency of this hormone causes the development of diabetes insipidus, manifested by polyuria and polydipsia [1, 2, 4, 7, 8].

Diagnosis

First of all, diagnosis is based on the detection of a history of the above etiological factors — trauma, neurosurgery, radiation, disease of the hypothalamic-pituitary area of inflammatory, infiltrative nature, etc. Progressive decrease in visual acuity and/or narrowing of the visual fields may be a symptom of a pituitary tumor. Ischemia of the pituitary, as the cause of pituitary insufficiency, may be indicated by massive bleeding during childbirth. Hemorrhage in the pituitary gland, or apoplexy, is characterized by an episode of sudden severe headache with marked well-being impairment.

Attention should be paid to such complaints as menstrual disorders in women and sexual dysfunction in men, as well as general weakness, decreased muscle strength, drowsiness, memory disorders, poor appetite, and increased fatigue, the severity of which increases by the end of the day and during exercise.

On examination, dryness and pallor of skin, bradycardia, orthostatic hypotension, increase in visceral fat and decrease in muscle mass, reduction of pubic hair, atrophic changes in the genital organs, breast hypoplasia in women and gynecomastia in men are diagnostically significant.

It must be emphasized that adrenal insufficiency poses the greatest threat to a patient who may need urgent therapy. In severe cases, the diagnosis of hypocorticism is primarily based on clinical manifestations, among which the most typical are poor appetite, weight loss and a decrease in blood pressure.

The main manifestations of diabetes insipidus are thirst and polyuria from 3 to 18 l/day. For brain injuries and surgeries, diabetes insipidus may be transient and can be resolved within 3–6 months. Concomitant adrenal insufficiency masks the symptoms of diabetes insipidus, since glucocorticoids contribute to water excretion by the kidney, while compensation for hypocorticism in such cases leads to increased polyuria.

The insufficiency of the tropic hormones of the pituitary gland is confirmed during laboratory studies. Considering the previously noted sequence in the damage of tropic functions, assay of the blood levels of insulin-like growth factor (IGF-1), LH, FSH, free thyroxine (FT4), TSH, and testosterone in men is recommended as disease screening.

The extent of laboratory studies necessary to confirm GH deficiency depends on the level of IGF-1 and the severity of damage to the hypothalamic-pituitary region. Detection of low levels of IGF-1 against the background of irreversible organic hypothalamic-pituitary damage with a decrease in the secretion of three other tropic hormones is a sufficient basis for the diagnosis of growth hormone insufficiency. It should be taken into account that the normal concentration of IGF-1 does not exclude the deficiency of GH (in 20–30 % of adults this figure may be within the reference range). In these cases, it is necessary to study the blood level of GH during a stimulation test, since the secretion of somatotropin has an impulsive nature and the assay of its basal level is not informative.

In patients with irreversible organic damage to the hypothalamic-pituitary region and a decrease in secretion of two other tropic hormones, the

secretion of GH is analyzed using one stimulation test. For suspected isolated GH deficiency, or combined with one or other tropic hormone deficiency, two stimulation tests are required.

For this purpose, insulin is most often used; the development of hypoglycemia during its administration provokes secretion of hypothalamic GH-releasing hormone, as well as clonidine, a centrally acting adrenergic agonist. The insulin hypoglycemia test is considered to be the "gold standard", but it is dangerous for patients with cardiovascular disease and with a tendency to convulsions. Tests with arginine, glucagon and somatoliberin may be an alternative. Arginine suppresses secretion of somatostatin, the mechanism of action of glucagon is determined by development of late hypoglycemia, and somatoliberin is a hypothalamic releasing factor, and unlike other tests, the use of the latter is not accompanied by side effects.

The most physiological assessment of somatotropic function is daily monitoring of GH secretion and determination of its nocturnal production, but due to the high cost, such studies are carried out in research centers.

GH-insufficiency requires confirmation both in adult patients with hypothalamic-pituitary diseases and in case of growth hormone deficiency from childhood or adolescence. Integrity of GH production should be assessed after compensation of the thyroid state. In the case of brain injuries and subarachnoid hemorrhage, a transient disorder of somatotropic function is possible. Therefore, its study is conducted one year after these events.

To assess the gonadotropic function, the levels of LH, FSH, as well as estradiol in women and testosterone in men are analyzed. Hypopituitarism is characterized by a decrease in the concentration of peripheral sex hormones in combination with a low or normal content of gonadotropins. In women of reproductive age, changes in the level of these hormones can be poorly manifested. In these cases the diagnosis of a deficiency of sex hormones is based on data from a gynecological examination.

Thyroid deficiency is confirmed by TSH and FT4 reduced blood concentration. In some cases, the level of TSH may be within the normal range and even slightly higher, but attention should be paid to its inadequacy to the low content of FT4.

To detect ACTH deficiency, it is recommended to evaluate the blood cortisol content during stimulation tests, since the assay of the basal cortisol level is not always informative. Insulin, Metopirone and tetracosactide (1–24 ACTH) are used as stimulants. The stimulating effect of insulin is determined by the development of hypoglycemia (2.2 mmol/l), on the background of which cortisol content should exceed 500–550 mmol/l. Metopirone blocks the enzyme of steroidogenesis (11-beta-hydroxylase), which causes a decrease in cortisol production to 140 nmol/l or less, and as a result, an increase in ACTH secretion of more than 150 pg/ml. Tetracosactide is a synthetic analogue of natural corticotropin, consisting of the first 24 amino acids of its molecule. After its administration the level of cortisol must be above 750 nmol/l. The advantages of the latter test include the absence of side effects, while conducting an insulin test may be complicated by the development of severe hypoglycemia, seizure syndrome, and acute adrenal insufficiency. Side effects of Metopirone test include nausea.

In the case of surgery for pituitary adenoma, there is a recommendation to determine morning blood cortisol on the 3rd day after surgery. It is shown that cortisol level above 15 μg/dl allows to exclude adrenal insufficiency.

Diabetes insipidus is characterized by hypernatremia, increased blood osmolarity, as well as by low relative density of urine (less than 1,005 g/l) and urine osmolarity (less than 300 mOsm/kg).

Laboratory research in hypopituitarism also includes clinical and biochemical blood tests, in which attention should be paid to the parameters of red blood cells, lipid profile, glucose, electrolytes, liver enzymes and nitrogenous waste. In addition, the analysis of daily fluctuations in blood glucose, which, in case of hypocorticism, is characterized by monotonic low or low-normal values, the so-called "flat sugar curve", is diagnostically valuable.

It should be emphasized that the clinical symptoms of the disease are of paramount importance for the diagnosis, which is either confirmed or rejected on the basis of hormonal studies.

The main method of instrumental diagnosis of hypopituitarism is magnetic resonance imaging (MRI) of the brain. With a disease duration of more than a year, osteodensitometry is recommended.

In the course of diagnosis of the disease, consultation of an ophthalmologist in case of visual impairment, as well as a gynecologist for women and an andrologist for men, is necessary.

When describing the diagnosis, the damage to peripheral endocrine glands is listed in the order of clinical significance: hypocorticism, hypothyroidism, and hypogonadism [5, 7, 9, 11].

Treatment

If in patients with hypopituitarism a space-occupying lesion in the chiasmatic-sellar region is detected, surgery may be necessary.

Conservative treatment is aimed at compensation for hormonal deficiency. Taking into account the clinical significance of endocrine disorders, their correction is carried out in the following sequence — first, compensation of adrenal insufficiency, then thyroid, gonads and GH insufficiency. For replacement therapy of adrenal insufficiency, natural glucocorticoids — hydrocortisone and cortisone acetate, as well as a semi-synthetic analogue, prednisolone, are used. The drug of choice is hydrocortisone, which is an analogue of the cortisol molecule, the main endogenous glucocorticoid. Cortisone acetate is a precursor of hydrocortisone and its activity is somewhat lower, since the action is manifested after a number of transformations in the liver. The need for glucocorticoids in secondary genesis of adrenal insufficiency is somewhat lower than in primary hypocorticism. Thus, in the onset of the disease, it can be 5–10 mg of hydrocortisone or 6.25–12.5 mg of cortisone acetate in single daily dose taken in the morning. If necessary, the dosage is increased and prescribed in 2–3 doses, taking into account the daily rhythm of cortisol, according to which 2/3 of the daily dose is recommended to be taken in the morning, from 8 am to 12 pm. The daily dose of hydrocortisone usually does not exceed 20 mg, which corresponds to the amount of cortisol produced in healthy people. In stressful situations, the dose of glucocorticoids is increased by 1.5–2 times and, if necessary, administered parenterally. In case of secondary hypocorticism, mineralocorticoids, as a rule, are not required, since the secretion of aldosterone largely depends on renin.

The effectiveness of treatment is evaluated clinically — by the absence of symptoms of hypocorticism, while the study of the level of cortisol and ACTH is not advisable.

Treatment of secondary hypothyroidism is carried out after compensation of adrenal insufficiency. For this purpose levothyroxine sodium preparations are used. The initial dose is usually 25 μg, which is gradually increased under the control of the blood level of FT4 until its normalization, which is a criterion for the effectiveness of treatment. TSH assay is not diagnostically informative. In the future, an annual blood test for the content of FT4 is recommended.

Replacement therapy with sex hormones is indicated in most cases of hypopituitarism. It is carried out after the compensation of adrenal and thyroid insufficiency. For women, the use of analogues of natural estrogens (estradiol) and progestogens (progesterone, dydrogesterone) is recommended, and the regimen of administration and dosage depend on age. Up to the age of 45 years, the drugs are prescribed in a cyclic mode: in the first two weeks of the menstrual cycle, estrogen 1–3 mg/day (per estradiol), and in the second two weeks — in combination with gestagen. For over 45–50 years of age, a monophasic treatment regimen is recommended: daily estrogen 1–2 mg/day in combination with a gestagen, the dose of which also decreases about 2 times.

Estrogen-containing medicines available exist in the form of oral preparations and transdermal gels. The advantage of the latter is the possibility of use in cases of pathology of liver, disorders of lipid and carbohydrate metabolism. In addition, the transdermal route of administration provides a more constant blood level of estrogen compared with oral forms. Gestagens may be prescribed for oral and intravaginal administration.

In cases where a woman has no uterus, only estrogen preparations (0.5–1.5 mg of estradiol) are prescribed, transdermal administration is preferred. In postmenopausal women, when relatively low doses of estrogens are required for replacement therapy, it is recommended to use oral medications, the bioavailability of which is relatively low due to rapid destruction in liver.

Treatment continues until the age of natural menopause, the average age for which is 51 years. In some cases, therapy may last up to 55–65 years, since postmenopause ends at 65–68 years.

Androgenic deficiency in men is eliminated by testosterone preparations for enteral, parenteral and transdermal administration. Testosterone undecanoate is taken orally, 40–80 mg 3 times a day, a mixture of testosterone esters — 1 ml IM every 2–4 weeks, a prolonged testosterone preparation,

the advantage of which is the absence of supraphysiological peaks of the blood hormone concentration — 1,000 mg IM every 3 months, a hydroalcoholic testosterone gel is applied to the skin at a dose of 50 mg daily. The advantage of short-term medicines is the possibility of their cancellation in case contraindications to androgen therapy is identified. Treatment of androgen deficiency in men is usually carried out for life.

The goal of sex hormone replacement therapy is to restore urinary functions, correct metabolic disorders, and maintain normal bone mineral density. When the recovery of fertility is required, treatment includes gonadotropin preparations that stimulate ovulation in women and spermatogenesis in men.

Unlike replacement therapy with glucocorticoids and thyroid preparations, treatment with sex hormones has contraindications. These are malignant neoplasms of the sexual sphere (uterus, ovaries, mammary glands in women; prostate and mammary glands in men), decompensation of liver and kidney function. In addition, contraindications to the use of sex hormone preparations in women are thrombotic diseases and the presence of a hormonally active pituitary tumor, and in men — benign prostatic hyperplasia with marked urethral obstruction.

Replacement therapy with sex hormones requires dynamic monitoring of the reproductive system status. For this purpose, women are subjected to ultrasound scanning of the pelvic organs (USS) every 6–12 months, as well as an examination of the mammary glands: at the age below 45, an ultrasound scan every 12 months, over 45 — mammography 1 time in 12–24 months.

In men, the first follow-up examination is recommended 1–3 months from the beginning of therapy to assess its adequacy and safety. The following assays are performed: blood testosterone levels (for parenteral administration — before the next injection), hematocrit and hemoglobin levels (hematocrit is above 55 %, and/or hemoglobin levels higher than 180 g/l are indications to reduce testosterone dosage), and a prostate-specific antigen concentration (more than 4 ng/ml requires cancellation of treatment and the patient should be examined by an urologist). The condition of the prostate gland is assessed by an urologist or andrologist according to the outcome of rectal examination and/or ultrasound. In future, such assessment is recommended every 6–12 months.

In some cases of hypopituitarism, replacement therapy with growth hormone is recommended, which is carried out after compensation of all other types of pituitary insufficiency. The indications are the clinical symptoms of GH deficiency and low levels of IGF-1 in the blood. An analogue of human growth hormone is used, its initial dose is 0.03–0.04 IU/kg body weight per week (0.4-0.5 IU/day), which, if necessary, is increased monthly by 0.2–0.5 IU. The average maintenance dose of growth hormone is about 0.125–0.25 IU/kg body weight per week (0.8–2.4 IU/day). With age, the need for growth hormone decreases, and elderly patients need more careful monitoring of treatment.

The main criterion of effectiveness is the level of IGF-1. It is assayed one month after each increase in the dose of the medicine, and with the achievement of the physiological values of this parameter, its monitoring is carried out once in 6–12 months. Against the background of therapy, a gradual, within 3–6 months, decrease in fat mass, an increase in muscle mass, an improvement in psychological status are observed; in some cases, such changes develop at a slower pace.

Contraindications for growth hormone replacement therapy include cancer, severe intracranial hypertension and proliferative diabetic retinopathy.

For replacement therapy in vasopressin deficiency, a synthetic analogue of its molecule with a less pronounced vasospastic effect, as well as greater antidiuretic activity and resistance to enzymatic destruction — desmopressin, is used in sublingual, oral and intranasal dosage forms. Adjustment of dosage is carried out clinically — based on the absence of symptoms of hormone deficiency (excessive thirst, polyuria) or overdose (edema, high blood pressure, reduced diuresis). The drug is administered 2–3 times a day, starting with minimal doses — 0.1 mg for oral tablets, 60 μg for sublingual tablets, 10 μg (1 dose) for intranasal spray or 5–10 μg (1–2 drops) for intranasal drops. Preference is given to sublingual tablets, which, unlike the oral form of the medicine, enter the bloodstream bypassing the liver, thus being effective at a lower dose, and unlike intranasal agents, their effectiveness does not change in case of catarrhal signs and chronic rhinitis.

Further monitoring of patients with hypopituitarism involves examination every 6–12 months, which includes an assessment of the clinical status of the above laboratory and instrumental data.

If space-occupying lesion of the hypothalamic-pituitary region is present, MRI of the brain is performed once in 6–18 months to exclude the growth of the pathological focus. Hypopituitarism due to the empty sella syndrome, irradiation of the hypothalamic-pituitary region, brain injury, pituitary infarction or lymphocytic hypophysitis does not require dynamic MRI monitoring of the brain [3, 6, 9, 12].

Prognosis

Adequate replacement therapy can restore normal health in patients with hypopituitarism. However, there is evidence of a twofold increase in mortality compared with the general population, the main causes of which are respiratory, cerebrovascular and cardiovascular pathology. The unfavorable factors of prognosis include female gender, the development of the disease due to craniopharyngioma and radiation therapy, a young age at the disease onset, and inadequate treatment.

Clinical Case

A 33-year-old female patient in July 2017 came with complains of headaches and reduced visual acuity. The examination revealed a hormonally inactive macroadenoma of the pituitary gland, based on which transsphenoidal adenomectomy was performed on 02.08.2017. Almost immediately after the operation, the headaches stopped, eyesight was restored, but appetite was lost; nausea and vomiting, thirst and polyuria, weakness appeared; the patient began to lose weight, which was regarded as a condition after surgery. Examination of the patient for adrenal insufficiency (blood cortisol level, endocrinologist consultation) was not carried out at that stage, apparently due to an underestimation of symptoms such as loss of appetite, dyspepsia, and fatigue. After discharge from the hospital, nausea and vomiting became more frequent, pains in the stomach appeared, the patient continued to produce large amounts of urine and drink a lot of water, weakness and weight loss increased, a deterioration of mood was observed, amenorrhea developed. Three weeks after the operation, the patient fell unconscious, and was taken by ambulance to the palliative care unit of the central regional hospital, where she stayed from 22.08. to 04.09.2017.

The examination showed a low specific gravity of urine (1,005 g/l, (1,009–1,025)), hypoproteinemia (58 g/l, (65–85)), and low-normal fasting glucose (3.87 mmol/l (3.3–5.5). Analysis of the blood electrolytes levels did not detect abnormalities: potassium — 3.8 mmol/l (3.5–5.5), sodium — 140 mmol/l (135–155). The study of the hormonal status revealed a decrease in the blood content of gonadotropins (FSH — 1.02 mIU/ml (2.8–11.3); LH — 0.92 mIU/ml (1.1-8.7)), TSH — 0.041 μIU/ml (0.23–3.5) along with a slight increase in the level of free thyroxine (FT4 — 2.01 ng/dl (0.8–1.9)). Prolactin concentration was 151 μIU/ml (40.3–530), and the growth hormone level was 0.4 ng/ml (0.06–5.0). On ECG — sinus bradycardia 40 in 1 minute.

The diagnosis was established: "Condition after removal of the pituitary macroadenoma. Alimentary exhaustion. Diffuse toxic goiter. Adrenal insufficiency?". Despite the suspected hypocorticism, cortisol levels were not examined.

Symptomatic (infusion of 10 % glucose solution, salt solutions, protein preparations, proton pump inhibitor, probiotic), as well as thyrostatic therapy — thiamazole 10 mg 2 times a day was prescribed with subsequent control of blood levels of TSH and FT4 in 2 months.

According to the patient, during two weeks of inpatient treatment, the state of health improved somewhat, but after discharge it began to deteriorate progressively again — there was a constant noise in the head, shortness of breath, she had to lie down almost all the time because of weakness, had no appetite, and continued to lose weight: 14 kg in 4 months after surgery.

On November 24, 2017, the patient was hospitalized to the Endocrinology Department of the G. G. Kuvatov RCH. According to the examination, there was a pronounced deficit of body weight (weight 41 kg with height 164 cm, body mass index — 15.5 kg/m^2), pallor and increased dryness of the skin, hypotension — 70 and 50 mm Hg, bradycardia of 45 beats per 1 min. According to the results of laboratory analyses iron deficiency anemia was revealed (red blood cells — 2.62*10^{12}/l (4.04–5.9), hemoglobin — 69.5 g/l (120–170), iron — 5.1 μmol/l (12.5–32.2)); hypoproteinemia (58 g/l (65–85)), hyperenzymemia (aspartate aminotransferase — 199.3 U/l (5.0-38.0), alanine aminotransferase — 128.8 U/l (5.0–42.0)), lack

of an adequate increase in the blood glucose level after a meal (daily glycemic fluctuations were 5.1–5.2–5.7 mmol/l). Blood electrolytes content was within the range of reference values (potassium — 3.7 mmol/l, sodium — 142 mmol/l). Urinalysis showed a low specific gravity — 1,005 g/l, Zimnitsky Urine Test did not exceed 1,000–1,002 g/l (1,009–1,025). According to hormonal analysis data, cortisol was 515.8 nmol/l (101.2–835.7), FT4 — 7.66 pmol/l (9.0–19.5). It should be noted that thyrostatic therapy was completed a month before this study, therefore its effect on the result was excluded. Repeated studies of the TSH level were not conducted, since the secondary genesis of hypothyroidism was obvious. Electrocardiography detected bradycardia (48 bpm) and significant diffuse disturbances of repolarization processes.

Considering the history of adenomectomy for pituitary macroadenoma, the development of typical clinical signs of adrenal and thyroid insufficiency (significant weight loss, lack of appetite, nausea, vomiting, pain in the epigastrium, severe hypotension and weakness, pallor and dry skin, bradycardia) and diabetes insipidus (thirst and polyuria), appeared after the surgery, data of hormonal blood tests (decrease of gonadotropins, TSH and FT4 levels), biochemical blood test (flat blood sugar curve, low levels of hemoglobin and iron, hyperenzymemia), urinalysis (low specific gravity), the following diagnosis was established: Postoperative hypopituitarism: secondary hypocorticism, hypothyroidism, hypogonadism. Diabetes insipidus. Complications: Iron deficiency anemia of moderate severity.

The severity of the patient's condition required the immediate prescription of glucocorticoids, in connection with which a decision was made on replacement glucocorticoid therapy, the positive effect of which from the first days of treatment convincingly confirmed the diagnosis established. During the first 5 days prednisolone was administered parenterally: for 3 days, 90 mg intravenously in the morning, 60 mg intravenously in the afternoon and 30 mg intramuscularly in the evening; the next 2 days the doses decreased to 60 mg intravenously in the morning and 30 mg intramuscularly in the afternoon and evening, and then 30 mg twice a day: intravenously in the morning and intramuscularly in the afternoon. Infusion therapy (5 % glucose solution, 0.9 % sodium chloride solution) volume was 2 liters per day. The patient was then switched to oral hydrocortisone — 10 mg in the morning and 5 mg after lunch with blood pressure monitoring. For the purpose of replacement therapy of vasopressin deficiency, desmopressin sublingual 60 μg was prescribed 2 times a day under the control of the fluid intake and output. On the seventh day of treatment with glucocorticoids, therapy was supplemented with levothyroxine at a dose of 25 μg in the morning. In addition, as an antianemic drug, the patient received iron (III) hydroxide polymaltose complex 100 mg 2 times a day.

During treatment, pain in the stomach, nausea and vomiting stopped, appetite was restored, weakness decreased, the patient began to gain weight, blood pressure and heart rate were normalized. According to the results of repeated laboratory analyses, normalization of protein levels in blood, transferases, positive changes in hemoglobin and iron content, as well as the achievement of reference urine specific gravity values were observed.

The patient was discharged home in a satisfactory condition with a recommendation to continue taking hydrocortisone at a dose of 10 mg in the morning and 5 mg after lunch under control of blood pressure, body weight and general well-being, levothyroxine at a dose of 25 μg in the morning, followed by determination of the blood level of FT4 after 1 month for dose adjustment if necessary, as well as desmopressin 60 μg 2 times a day under the control of urine output.

After compensation of thyroid status, consultations with a gynecologist and endocrinologist are recommended to decide on the prescription of sex hormone replacement therapy.

Commenting on the presented case, it would be desirable, first of all, to pay attention to the fact that after surgery the patient developed typical symptoms of pituitary insufficiency, of which the most pronounced were symptoms of adrenal hormone deficiency. And although this diagnosis was assumed, since it is indicated under the question mark in the discharge note from the hospital at the place of residence, the patient's condition and the results of the studies were regarded as a result of diffuse toxic goiter (DTG). Such a judgment seems to be related to the patient's complaint about losing weight and hormonal analysis data that revealed a decrease in TSH and an increase in FT4, which is characteristic of thyrotoxicosis. However, the

interpretation of the results of a hormonal study without a comprehensive analysis of the clinical picture caused an erroneous diagnosis and, accordingly, inadequate treatment, which led to further deterioration and re-hospitalization.

As regards DTG, its clinical manifestations are due to thyrotoxic hypersympathicotonia; therefore weight loss occurs due to increased metabolism, while a decrease in appetite is not characteristic. The clinical picture of DTG unfolds gradually; first neurological symptoms of hyperthyroxinemia prevail: anxiety, sweating, sleep disturbance, and tachycardia. In the described case, a decrease in strength and mood, lack of appetite and a decrease in body weight, bradycardia were observed, with the listed symptoms developing almost immediately after neurosurgical operation.

It should be noted that a reduced level of TSH was combined with a decrease in gonadotropins and signs of diabetes insipidus — polyuria, thirst and low urine density, which indicates the need to search for a single genesis of the identified changes. In this case, it is surgery on the pituitary gland with the development of hypopituitarism. As for the slightly increased level of FT4, detected 3 weeks after adenomectomy, this is apparently due to the body's response to a stressful situation.

Manifestations of glucocorticoid insufficiency are primarily explained by their influence on carbohydrate metabolism, namely, a decrease in glucose production, which causes the most characteristic symptoms of the disease, such as lack of appetite, weight loss, asthenization, tendency to hypoglycemia, which was the case in our patient.

The effectiveness of glucocorticoid replacement therapy convincingly confirmed the diagnosis of hypocorticism "ex juvantibus".

Thus, the priority of the clinical picture in the interpretation of the results of the examination of the patient is a fundamental principle, the use of which makes it possible to clarify many diagnostic situations which, at first glance, appear complicated. At the same time, the wide availability of various diagnostic manipulations in this day and age has the other side of the coin; their results may not only not solve the problem of diagnosis, but on the contrary, raise even more questions. In this regard, the words of the founder of clinical medicine in Russia Matvey Yakovlevich Mudrov "*Knowledge of the disease is half of the treatment*" become even more relevant.

Conflict of interests

The authors declare no conflict of interests.

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Article received on 14.01.2019
Accepted for publication on 13.02.2019