This paper presents the most common disorders of pituitary function: acromegaly, hypopituitarism, diabetes insipidus and syndrome similar to diabetes insipidus, in terms of their importance in preoperative preparation of patients. Pituitary function manages almost the entire endocrine system using the negative feedback mechanism that is impaired by these diseases. The cause of acromegaly is a pituitary adenoma, which produces growth hormone in adults. Primary therapy of acromegaly is surgical, with or without associated radiotherapy. If a patient with acromegaly as comorbidity prepares for non-elective neurosurgical operation, then it requires consultation with brain surgeons for possible delays of that operation and primary surgical treatment of pituitary gland. If operative treatment of pituitary gland is carried out, the preoperative preparation (for other surgical interventions) should consider the need for perioperative glucocorticoid supplementation. Panhypopituitarism consequences are different in children and adults and the first step in diagnosis is to assess the function of target organs. Change of electrolytes and water occurs in the case of pituitary lesions in the form of central or nephrogenic diabetes insipidus as a syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Preoperative preparation of patients with pituitary dysfunction should be multidisciplinary, whether it is a neurosurgical or some other surgical intervention. The aim is to evaluate the result of insufficient production of pituitary hormones (hypopituitarism), excessive production of adenohypophysis hormones (acromegaly, Cushing’s disease and hyperprolactinemia) and the influence of pituitary tumours in surrounding structures (compression syndrome) and to determine the level of perioperative risk. Pharmacological suppressive therapy of the hyperfunctional pituitary disorders can have significant interactions with drugs used in the perioperative period.

Key words: preoperative preparation, acromegaly, hypopituitarism, diabetes insipidus, SIADH

INTRODUCTION

Preoperative evaluation of patients with pituitary dysfunction means to determine preoperative hormonal status, body anatomical changes that may affect the choice of anaesthetic technique and testing the functional gland reserve using stimulation or suppression tests. Particularly important is to check the chronic specific therapy that can influence the choice of drugs used in the perioperative period. In addition to the many symptoms and characteristic look as a consequence to the functional disorders of the pituitary gland, these patients may have comorbidities that significantly increase perioperative morbidity and require special treatment. Pituitary lesions, which cause the most of cancers, may be with hormone hypersecretion or hyposecretion, tumour compression syndrome or incidentalomas (10% of patients undergoing cranial tomography). Assessment of patients with pituitary disease should include: hormonal pituitary status and target glands in which regulation it is involved, the signs of local compression syndrome, the presence of symptoms of intracranial hypertension and the presence of comorbidity. Of a great importance is the complete hormonal treatment of these patients, their appearance, physical examination, and if necessary, additional examinations neuro-ophthalmologist, cardiologists and radiologists. Nuclear magnetic resonance and the target tomography of the head are necessary in newly diagnosed diseases and sometimes in order to control the disease and treatment.
PITUITARY FUNCTION

Embryologically, histologically and functionally looking, pituitary gland is a bivalent organ. It consists of the anterior lobe (adenohypophysis) and posterior lobe (neurohypophysis).

ADENOHYPOPHYSIS

Adenohypophysis is secreting six hormones: growth hormone (GH) or somatotropic hormone (STH), adrenocorticotropic (ACTH), thyroid-stimulating (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin (PL). Apart from STH, which affects almost all body tissues, other adenohypophysis hormones affect the target glades. Clinical manifestations of adenohypophysis dysfunction depend on the target organ involved in impaired regulation. It can be expressed as hypofunctional or hyperfunctional disorder.

Increased secretion of adenohypophysis hormones is primarily a result of pituitary tumours (mostly adenomas), which represent 10% of intracranial tumours. Adenomas generally secrete a hormone, although there may be secretion of two or more hormones (GH and PL). Growth hormone increases the volume of all cells in the body and it causes miosis, too. Because of the progressive upward growth, pituitary tumours cause damage to the optic chiasm with visual loss. Headache is a common symptom. Other neurologic signs (vomiting, mental status changes, neurological disturbances, papilloedema) are rare. Diagnosis is based on clinical symptoms, radiography of the head, precise technique of magnetic resonance imaging (MRI) with contrast, targeted tomography (CT) and hormonal tests.

NEUROHYPOPHYSIS

Neurohypophysis secretes two hormones: antidiuretic hormone or vasopressin (ADH) and oxytocin. These hormones are actually synthesized in the hypothalamus, and they get to the back lobe of the pituitary gland via the portal vascular system where it is deposited in secretory granules. Decrease in plasma volume, pain, stress, sleeping, physical exercise, some drugs (opioid analgesics, intravenous and inhalational anaesthetics) stimulate the secretion of ADH. Plasma hypoosmolality, so as alcohol, exposure to cold, some medications (opioid antagonists) lead to the decreased secretion of ADH. Basic physiologic role of ADH is to increase the permeability of distal renal tubules to water.

ACROMEGALY

Acromegaly is the result of hypersecretion of STH in the period after the longitudinal growth of adults is completed. The most significant change is the bone-joint system. Hypersecretion of STH causes the growth of bones, cartilage and soft tissue through effects of insulin-like growth factor 1 (IGF-1), also known as somatomedin C. It is produced in the liver, kidneys and other tissues that respond to STH. Following the closure of epiphyseal cartilage, linear growth is not possible, so that the excess of STH leads to the enlargement of peripheral (acral) parts of bone, cartilage and soft tissue.

Metabolic effects of STH are numerous:

- Increased frequency of protein synthesis in all cells in the body
- Mobilization of fats with increased free fatty acids
- Decreased speed of utilization of glucose in the tissues through the decrease of cellular uptake of glucose (contraregulatory effect of insulin)
- Increased flow of glucose through the liver.
- Stimulation of erythropoiesis.
- Reduced excretion of Na⁺ and K⁺ while the absorption of Ca²⁺ from the intestine is increased.

Stimuli that increase the secretion of STH are divided into three general categories:

- Hypoglycaemia and starvation
- Increasing concentration of amino acids in plasma
- Stressor stimulus

STH secretion decreases in response to the increase:

- the concentration of glucose
- free fatty acids or cortisol in plasma,
- decreases during REM sleep stage and increases in the stage of deep sleep.

Effects on growth and metabolic changes in tissues are taking place slowly and the manifestation of clinical signs of that activity comes gradually.

Clinical picture of acromegaly develops slowly so that the patient’s appearance and changes may not be immediately visible. The disease usually begins in the third decade of life. It is represented in both sexes. It is characterized by excessive growth of connective tissue, internal organs, small and membrane bone growth which last for life. The distal parts of the body also increase: hands, feet, nose, frontal arcades, sinuses, jaw, causing the patient has a distinctive look. To stimulate growth of cartilage and bone leads to degenerative changes in joints. There is carpal tunnel syndrome due to reduced flow through the ulnar artery in some patients. Peripheral neuropathy is a common because of the nerve compression due to increased skeletal, muscle and connective tissue. Enlargement of the visceral organs leads to hepatosplenomegaly, cardiomegaly, enlargement of the glandular tissue, macroglossia. Due to reduced utilization of glucose, there is hyperglycaemia, insulin resistance, and over time, diabetes mellitus in 10% of patients with acromegaly. Hyperphosphataemia is a consequence of increased absorption of phosphate in the kidney under the effect of STH. Lipolysis leads to increased free fatty acids in the blood. With one third of patients pituitary tumour also secretes prolactin, leading to galactorrhea, amenorrhea, and loss of libido.

Because of the expansive growth of the tumour compression syndrome with blurred vision may arise, so as headache, change of rhythm sleep, appetite and body temperature. Unless adequate treatment is taken (hormonal or surgical), expansive tumour growth may lead to the destruction of the remaining pituitary tissue with the appearance of hypopituitarism.
Primary therapy of acromegaly is surgical, with or without associated radiotherapy. If a patient with acromegaly as comorbidity is being prepared for nonelective neurosurgical operation, it requires consultation with brain surgeons for possible delays that operation and primary surgical treatment of pituitary gland. If operative treatment of pituitary gland is carried out, the preoperative preparation (for the second surgical intervention), should consider the need for perioperative glucocorticoid supplementation.

Some patients respond well to medical therapy (bromocriptine, somatostatin analogues, receptor antagonists STH), so we established normal levels of hormones without surgery. Medical therapy of acromegaly is long-term, and can lead to relapse with increasing levels of STH and re-expansion of the tumour.

Preoperative evaluation of the patient should focus on mobility and airway management. Excessive GH can produce soft tissue hypertrophy of the mouth, nose, tongue, gums, and soft palate, epiglottis and aryepiglottic folds. Hoarseness indicates the existence of laryngeal stenosis due to thickening of the vocal cords. The deformation of the face and bone structure that causes prognathia which together with macroGLOSSIA often leads to occlusion of the mouth. About 25% of patients with acromegaly have the thyroid gland enlarged with compression of the trachea. Mask ventilation and tracheal intubation can be difficult. Careful assessment of airways includes, conventional criteria for DI and radiography neck and chest. Based on overall analysis of the results, the decision should be made on the technique of securing the airway during surgery by direct laryngoscopy with endotracheal intubation, awake fibreoptic intubation or surgical elective tracheotomy.

Southwick and Katz have defined four levels of airway changes in patients with acromegaly:
1. No change.
2. Hypertrophy of the nasal and pharyngeal mucosa, but with normal vocal cords and larynx.
3. Stenosis of the larynx or vocal cord paresis.
4. The combination of the second and the third level.

Elective tracheotomy for the 3 and 4 level changes has been recommended.

Patients with acromegaly have often sleep apnea, and in the postoperative period it is required to continuously monitor the consciousness and respiratory function.

In the preoperative preparation it is of great importance to correct the metabolic disorders, blood glucose regulation and cardiovascular disorders. In elderly patients to whom the disease is diagnosed too late, systemic hypertension is present, so as cardiomegaly, congestive cardiac failure. Cardiomyopathy with cardiomegaly requires cardiovascular assessment, including ECG, chest radiography and echocardiography. Pharmacological treatment of acromegaly before the surgery can greatly reduce the disorders previously mentioned, but it has numerous side effects (see later). Patients with chronic obstructive sleep apnea may have signs of right heart failure due to pulmonary hypertension. Diabetes mellitus or impaired glucose tolerance associated with acromegaly require preoperative insulin therapy.

In the preoperative treatment for non-neurosurgical intervention, and often as a permanent therapy in case of inoperable tumours, patients with acromegaly receive suppressive hormone therapy, which demands the good knowledge of the subject. The therapy includes three groups of drugs: dopamine agonists, somatostatin analogues and analogues GH. The choice of drugs depends on the reaction of patients, availability of the products and their prices. Pharmacological treatment of acromegaly with dopamine agonists (bromocriptine, cabergoline, and pergolide) relieves the symptoms of acromegaly and reduces the concentration of GH but normalizes the level of IGF-I with only 10% of the patients. Bromocriptine mesylate is a dopaminergic agonist that activates the post synaptic dopamine receptors. This drug causes numerous side effects such as hypertension, convulsions, heart attack, and stroke. Side effects that occur in acromegaly patients undergoing therapy are: nausea (18%), constipation (14%), orthostatic hypotension (6%), anorexia (4%), dry mouth, nasal congestion (4%), dyspepsia (4%), digital vasospasm (3%), fatigue (3%) and vomiting (2%). Although rare (less than 2%), severe disturbances are possible in the form of: gastrointestinal bleeding, dizziness, exacerbation of Ryan’s syndrome, headache and syncope. Risks of using bromocriptine in combination with other drugs have not been systematically investigated, but it is proved that alcohol emphasizes the side effects of the drug. Drugs that reduce the efficiency are: phenothiazines, haloperidol, metoclopramide, pimozide. Bromocriptine is a substrate and inhibitor of CYP3A. Therefore, caution is required with coadministration of drugs which are strong inhibitors or substrates of these enzymes such as azole antifungals and HIV protease inhibitors. Concomitant use of macrolide antibiotics may increase plasma concentrations of bromocriptine. Joint use with ergotamine alkaloids is not recommended due to strong peripheral vasospasm especially in the cold. Somatostatin analogs repel the secretion of GH by binding to the receptors of somatostatin, and they are applied with a patient who badly responds to therapy of dopamine agonists. These drugs achieve GH concentrations below 2 mg/l (5 mIU/l) in 60% to 70% of patients, and normalization of IGF-1 levels in 50% to 80% of patients. In addition to antisecretory effects, somatostatin analogues reduce the volume of tumours (mainly the suprasellar part) with 20% to 70% of patients. Reduction in tumour volume is greater when somatostatin analogues are the first line treatment. In certain cases (contraindications for surgery, patients with severe comorbidities that need to prepare for surgery, invasive tumours whose removal is unlikely) somatostatin analogues may represent the first line therapy. The disadvantages of this therapy are reflected in long-term use and side effects of which the most important is nephrolithiasis of the gall bladder described in 10% to 20% of patients.
In preoperative preparation of patients with acromegaly the drug therapy should be reduced in terms of dose and drug choice should be made based on a minimum of side effects and simple parenteral dosage (Octreotide or Pegvisomant)\textsuperscript{9,10}.

**HYPOPITUITARISM**

Hypopituitarism is a syndrome of loss of function of all glands that are under the stimulatory effect of pituitary gland hormones. Damage to the pituitary gland may cover only a particular zone (monotropic hypopituitarism) with the damage of secretion of certain hormones, but more often it is the cause of diffuse process involving the entire gland creating a generalized adenohypophysis hormone deficiency (panhypopituitarism). The most often it is a progressive process so that partial hypoparathyroidism gradually transits into panhypopituitarism over many months or years. At first the decreased secretion of GH occurs, and then LH, FSH, TSH, ACTH. The three main mechanisms lead to the appearance of hypoparathyroidism. The first involves reducing the hypothalamus realising hormones that stimulate pituitary gland function. The cause may be congenital or the result of the tumour, inflammation, infections, compression tumour mass or circulatory disorders in the region of the hypothalamus. Another reason is the events that prevent the release of hormones from the hypothalamus. One such case is the appearance of a tumour or aneurysm of hypothalamic region. The damage of the pituitary stalk during surgery is also a possible cause. The third cause of hypopituitarism is the destruction of the pituitary gland due to tumour that originates from the anterior part and its expansive growth impairs the production of other adenohypophysis hormones\textsuperscript{11,12}.

In childhood, this deficiency is manifested in growth retardation with hypogonadism, hypothyroidism and hypoadrenalinism. Less common is the case where only the growth hormone lacks, with normal secretion of other adenohypophysis hormones, and that condition is manifested only as a profoundly short stature (namosmia pituitaria). As a primary pituitary gland disorder in the growth retardation with children may be due to primary destruction of the pituitary gland or congenital lesions of the pituitary gland or hypothalamus. This disorder is very rare (1:1000 to 1:10,000 population). Mostly it is about the destructive lesions of the hypothalamus or pituitary gland, which includes craniopharyngioma, trauma, granulomatous infiltrates and pituitary gland tumours. Hypopituitarism of childhood is manifested starting from the fourth or fifth year of life. The growth of the dwarf does not exceed 138 cm. The body is mostly straight and symmetrical structure. In adulthood, these patients have the infantile built body, the colour of children’s voice, lack of secondary sexual characteristic, but intellectual abilities are not damaged. In addition to hypogonadism, there is a decreased resistance to infection and stress, insulin sensitivity and tendency to hypoglycaemia. Difficult intubation with these patients has been described for several reasons. Infantile larynx makes the passage of the tube more difficult and it has a small diameter. Spondiloepiphyseal dysplasia with scoliosis of the neck makes difficult the neck mobility, and there are numerous abnormalities of the cervical spine, such as congenital absence of odontoid protrusion. Abnormalities of lung function as mucopolysaccharidosis may compromise the airways. Hypersensitivity to general anaesthetics is much expressed. Substitution of all target organs hormones is usually lifelong.

Hypopituitarism in adults is mainly manifested as an acute disorder, usually because of vascular lesions with a dramatic picture in the case of pituitary apoplexy\textsuperscript{12,13}. Pituitary apoplexy can occur spontaneously with patients with pre-existing pituitary gland tumour (usually non-functional) post partum (Sheehan’s syndrome - pituitary gland hyperplasia during pregnancy increases the risk of haemorrhage and infarction) or associated with other diseases (including diabetes mellitus, hypertension, anaemia sickle cell, radiotherapy, surgery, open heart surgery or acute shock). Clinical picture of pituitary apoplexy is manifested with: a strong headache, visual impairment, ophthalmoplegia, which changes over time, meninigism and altered states of consciousness and cardiovascular collapse. Urgent therapy involves the use of high doses of corticosteroids (dexamethasone 2 mg at 6 h) and transphenoidal decompression of intrasellar content that saves the life of a patient and prevents from permanent damage (vision loss)\textsuperscript{14,15}

Simmonds disease is characterized by a complete deficiency of adenohypophysis hormone secretion\textsuperscript{16}. Patients are extremely thin (Simmonds cachexia), adynamic, slow, sleepy, with the slow passage of intestinal that slowly reacts to external stimuli. Their skin is cold, pasty, rough. They are sensitive to cold, unresisting to trauma and infection. Amenorrhea with women, the absence of hairiness with men and genital atrophy is present. Insufficiency of ACTH requires the substitution of glucocorticoids in order to prevent adrenal crisis. Clinical manifestations of the secondary adrenal insufficiency (as part of hypopituitarism) are somewhat different from those of the primary adrenal insufficiency (due to diseases of the adrenal cortex). The concentration of ACTH (the melanocyte stimulating hormone MSH that arises from the same precursor) is low in the secondary adenal insufficiency and hyperpigmentation does not occur\textsuperscript{17}. Changes of electrolytes in terms of hyperkalemia and hyponatremia are minimal in secondary adrenal insufficiency because the aldosterone secretion, which is not ADTH-dependent, is preserved\textsuperscript{18}. The substitution of thyroxine in doses of 50-150 mg per day is necessary. The substitution of sex hormones is also necessary with young people. However, the patients with panhypopituitarism are exposed to a higher risk and complications during life in the case of infectious disease, injury or surgical intervention\textsuperscript{19}.

The preoperative preparation, besides the access to hormone therapy, the orderliness of its application and the control of hormonal status, to the patients with panhypopituitarism it is necessary to increase doses of medication due to reduced hormonal and metabolic response to stress. This applies primarily to the increasing corticosteroid doses and thyroid hormones. Patients with panhypopituitar
tarin are subject to water intoxication and hypoglycæmia. Patients are sensitive to sedatives and general anaesthetics, and because of hemodynamic instability they require circulatory support with vasoactive drugs. Continuous monitoring of cardiovascular function, hourly diuresis, fluid balance measurement, the concentration of electrolytes in these patients is of vital importance.

**DIABETES INSIPIDUS**

Diabetes insipidus is a clinical syndrome characterized by excretion of large amounts of diluted urine, which is a result of decreased secretion of ADH (hypothalamic diabetes insipidus) or due to lack of response of renal tubules in a normal amount of ADH (nephrogenic diabetes insipidus). Causes of hypothalamic insipidus diabetes are: surgical lesions of supraoptic tract above the median eminence, trauma, tumours, and infiltration of the hypothalamus using leukemic cells, granulomas, histiocytes or infectious abscesses, family and idiopathic. Rarely is the cause lesion of the posterior pituitary gland

Causes of nephrogenic diabetes insipidus are: congenital (X-linked transmission) and acquired (hydroproteinemia, electrolyte imbalance, drugs, chronic renal disease).

The basic criteria for the diagnosis of hypothalamic diabetes insipidus are: decreased secretion of ADH despite hyperosmolarity of the serum and urine osmolarity increased in response to exogenous ADH. Clinical picture is dominated by polyuria, with urine volumes of 3-15 litters per day and polydipsia. Enhanced fluid intake because of the strong feeling of thirst will maintain the hydration and prevent the formation of hyperosmolar syndrome as long as patients are aware. However, in comatose patients and in young children it may lead to quick life-threatening dehydration which is followed by hyperosmolar plasma and cardiovascular collapse. Therapy involves the correction of intravascular volume with the infusion of hypotonic fluid, and the infusion rate depends on the intensity of clinical symptoms. It is necessary to correct plasma osmolality mOsm speed of 1-2 mph, no faster than 15 mOsm during 8h (30 mOsm in the first 24 hours). It is also necessary to adjust the total water deficit for the first 48 hours. Desmopressin acetate is used in the dose of 1-2 µg for 24 hours (IV or IM), if the diagnosis of central diabetes insipidus is confirmed (with nephrogenic diabetes insipidus chlorpropamide is given).

**SYNDROME OF INAPPROPRIATE ADH SECRETION (SIADH)**

Syndrome of inappropriate secretion antidiuretic hormone (SIADH) or Schwartz–Bartert syndrome is characterized by persistent ADH secretion and excretion of concentrated urine despite the serum hypooosmolarity. This syndrome is followed by hyponatremia, serum hypoosmolality, continuous excretion of sodium despite hyponatremia, urine osmolarity which is greater than serum osmolality, adjustment of symptoms by reducing the water intake.

The causes of this syndrome are numerous:

- Pulmonary disease - some lung cells (it is not yet clear which ones) can secrete ADH in conditions of inflammation or infection.
- Cancer-differently located tumours which release ADH, usually small lung cells cancer.
- CNS diseases - infections, tumours, stroke.
- Drugs - Many drugs can affect (barbiturates, morphine, nicotine, oxytocin, thiazide diuretics, etc.)
- Stress (because of surgery or trauma).
- Other endocrine disorders (hypothyroidism, pituitary gland insufficiency).

Criteria for the diagnosis of SIADH are:

- Low serum osmolality and hyponatremia,
- Urine that is submaximally diluted,
- Urinary sodium excretion which matches the intake,
- Absence of other causes of abnormal urine dilution,
- Improvement of hyponatremia after water intake restrictions.

Symptoms of the disease are the consequence of hyponatremia. They occur only when serum sodium concentration falls quickly below 125mmol/l. The most prominent symptoms are: headache, anorexia, nausea, vomiting, confusion, disorientation, aggression, convulsions and coma.

Cardiovascular disorders in the form of arrhythmia are also present.

The cause of SIADH should be treated whenever possible. However, if this disorder occurs within the surgical intervention in the perioperative period, the therapy of SIADH consists of SIADH fluid restriction, diuretics application (furosemide), compensation of potassium, calcium and magnesium. If a hyponatremia is severe (below 120 mg/dl), hypertonic sodium chloride (3%) should be administered, in a slow IV infusion (at a rate of 0.1 ml/kg/min). It is recommended the correction of serum sodium by 0.5 mmol/L/h. Drugs that reduce the effect of vasopressin on the kidney (300mg of demeclocycline three to four times a day) inhibition of responses of renal tubules to ADH. Monitoring of renal function and the concentration of nitrogen compounds in the blood is necessary.

**CONCLUSION**

Patients with pituitary gland disorder can have increased perioperative risk because of disturbed homeostasis of the whole endocrine system. Frequency of pituitary gland diseases is not high, but perioperative preparation requires great knowledge of regulative control mechanisms for pituitary gland hormone secretion and also for target glands. Pituitary gland disorders can be in the forms of gland hypofunction or hyperfunction. Steady-state hormone status regulation with substitution or suppressive therapy is necessary. Elimination of all medicaments which can be in interaction with existing therapy if it is possible by decrease of the medicaments doses to prevent their toxic effects on other organs. Stress hormone doses increase in perioperative period in patients with panhypopituitarism is essential.
**SUMMARY**

**PREOPERATIVNA PRIPREMA BOLENIKA SA POREMEĆAJEM FUNKCIJE HIPOFIZE**

U radu su prikazani najčešći poremećaji funkcije hipofize: akromegalija, hipopituitarizam, dijabetes insipidus i sindrom sličan dijabetesu insipidusu, sa aspektima njihovog značaja u preoperativnoj pripremi bolesnika. Hipofiza upravlja funkcijom gotovo celokupnog endokrinog sistema mehanizmom negativne povratne sprege koja je u navedenim oboljenjima narušena. Uzrok akromegalije je pituitarni adenom koji produkuje hormon rast koji može dovesti do ozbiljnih komorbiditeta. Priprema bolesnika za akromegalijom kao komorbiditetom, priprema za neuro-hipofize, preoperativna priprema preoperativnom periodu, potrebna je konsultacija sa neurohirurzima radi eventualnog odlaganja te operacije i primarnog ope

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