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VIOLATION OF CARBOHYDRATE METABOLISM IN CUSHING'S SYNDROME

Yulduzkhan Kholmatova,
Master's Student of Tashkent Pediatric Medical Institute
G.J. Narimova, H.Q. Nasirova,
Doctor of Medical Sciences, Tashkent Pediatric Medical Institute, Uzbekistan

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Abstract:

Analysis of the rhythm and level of incretin secretion in patients with acromegaly and Itsenko-Cushing's disease (ICD), depending on the identified disorders of carbohydrate metabolism.

Keywords: Acromegaly, It Senko-Cushing's Disease, Disorders Of Carbohydrate Metabolism, Incretins, Neuropeptides.

INTRODUCTION

Today, in clinical practice, erased forms of endogenous hypercortisolism are increasingly encountered, which are manifested by nonspecific symptoms, namely arterial hypertension, diabetes mellitus, obesity. Taking into account the high risk of cardiovascular mortality in patients with hypercortisolism, the timeliness of making a true diagnosis is important.

A clinical case of Itsenko-Cushing's disease is presented, which manifested itself in the development of diabetes mellitus, arterial hypertension, rapid weight gain, without characteristic skin symptoms of the disease. Timely surgical treatment led to a complete regression of diabetes mellitus, normalization of blood pressure and body weight of the patient.

MATERIALS AND METHODS

Acromegaly and Itsenko-Cushing's disease (BIK) are the most severe neuroendocrine diseases that develop as a result of excessive production of growth hormone and adrenocorticotropic hormones by a pituitary tumor. Intermediate metabolism of carbohydrates is understood as the processes of their transformations in tissues, closely related to protein and lipid metabolism and aimed both at creating conditions for maintaining adequate energy metabolism and at the formation of a number of compounds necessary for the body. The latter include pentose phosphates (used for the synthesis of nucleotides and NADPH), as well as numerous heteropolysaccharides that act as neurotransmitters in the body (acetylcholine), antioxidants (glutathione), biologically active substances (heparin and other proteoglycans), secretory components (mucopolysaccharides), etc. ...

The following processes and conditions can be mentioned as examples of manifestations of disorders in the intermediate metabolism of carbohydrates: - increased glycolysis under conditions of hypoxia; - inhibition of the formation of acetyl-CoA; - abnormal changes (excessive increase and decrease) in the activity of gluconeogenesis; - defects in the pentose phosphate pathway of carbohydrate utilization. In hypoxic conditions (against the background of general insufficiency of blood circulation, respiration, with severe anemia, etc.) due to the predominance of anaerobic respiration over aerobic respiration, an excessive accumulation of lactic and pyruvic acids occurs, which provokes tissue acidosis. Excessive mobilization of glycogen as a source of glucose under conditions of its ineffective anaerobic utilization leads to depletion of glycogen stores during chronic hypoxia, which further contributes to hypoglycemia. Blocking the formation of acetyl-CoA leads to a violation of the interconversions of carbohydrates, fats and proteins, since all such interconversions must go through the intermediate stage of acetyl-CoA.

The latter is formed in mitochondria as a result of oxidative decarboxylation of pyruvic acid. Hypoxia, arsenic intoxication, some hypovitaminosis (for example, lack of vitamin B1 - thiamine) damage the pyruvate dehydrogenase system and reduce the synthesis of acetyl-CoA. Because of its universal role, it is reflected in a variety of cells, tissues and organs - from red blood cells to the central nervous system. Deviations in the activity of gluconeogenesis always noticeably affect the level of glucose in the body.

This process is an additional source of endogenous glucose due to its synthesis from glycogenic amino acids (alanine, 8 glycine, serine, etc.), lactic and pyruvic acids, glycerol and a number of other compounds in liver and kidney cells. Gluconeogenesis is mainly activated (enhanced) in cases where the utilization of glycogen is insufficient to maintain blood glucose levels that can meet the needs of the

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body. Similar cases are observed during periods of prolonged fasting, with prolonged and hard physical work.

The main hormonal stimulants of gluconeogenesis are glucocorticoids and glucagon. Adrenaline, growth hormone and thyroid hormones also contribute to the activation of gluconeogenesis, since they increase lipolysis, i.e. increase the level of fatty substrates that are converted into carbohydrates. An increase in the production of these hormones is accompanied by an increase in gluconeogenesis and, as a consequence, hyperglycemia. The downside of enhanced gluconeogenesis is the catabolism of fats and proteins (in lymphoid tissue, skin, muscles), which supplies substrates for glucose synthesis. Inhibition of gluconeogenesis with the development of hypoglycemia is noted with a deficiency of the above hormones, with excessive production of insulin (with insulinoma), as well as with severe liver damage.

Violations of the pentose cycle of glucose oxidation can be acquired (with a deficiency of vitamin B1, when the formation of ribose is impaired) or congenital. Among congenital defects of the pentose-phosphate shunt, the most common deficiency or abnormality of glucose-6-phosphate dehydrogenase. At the same time, the necessary restoration of glutathione, which is the most important factor in antioxidant protection, is not provided. In the erythrocyte membrane, glutathione deficiency is accompanied by the activation of lipid peroxidation, which entails an increase in membrane permeability and hemolysis (hemolytic anemia occurs, which is related to hereditary enzymopathies).

The severity of the course of acromegaly and NIK is primarily due to the development of multiple complications that complicate the radical treatment of the disease, leading to the disability of patients and, in some cases, even death.

Itsenko-Cushing's disease is a rather rare, but severe disease along the course, accompanied by the development of metabolic, cardiovascular, cognitive and psychological disorders.

Diabetes mellitus (DM) is one of the most common complications of hypercortisolism (from 20 to 50% of patients); impaired glucose tolerance occurs in almost 70% of patients. The main causes of hyperglycemia are the activation of key gluconeogenesis enzymes in the liver under the action of glucocorticoids and an increase in insulin resistance due to impaired transmission of the insulin receptor signaling pathway, activation of lipolysis and proteolysis. Age, genetic predisposition and lifestyle also play a significant role in the development of disorders of carbohydrate metabolism in patients with hypercortisolemia .

The optimal type of treatment for Itsenko-Cushing's disease is a neurosurgical operation (transnasal adenomectomy) . However, complications of hypercortisolemia, especially long-term, may not be regressed after achieving remission of the underlying disease.

The relevance of studying carbohydrate metabolism in patients with acromegaly and BIK is explained by both the frequent occurrence of glucose metabolism disorders and the difficulties in selecting sugar-reducing therapy in these categories of patients. The effectiveness of the treatment of hyperglycemia in such patients is most often reduced due to the difficulty of achieving compensation for the underlying disease, as well as due to the use of specific therapy that promotes the development of hyperglycemia.

In recent years, close attention has been focused on the study of the physiology of incretin hormones (hormones of the gastrointestinal tract involved in the regulation of glucose metabolism) and their secretion under conditions of various disorders of carbohydrate metabolism.

A detailed study of the incretin system in patients with "secondary" diabetes mellitus, including in patients with neuroendocrine diseases, has not been carried out. Determination of the features of the secretion of incretin hormones in conditions of excess cortisol and growth hormone / insulin growth factor-1 can determine the place of incretin-targeted therapy - type 4 dipeptidyl peptidase inhibitors and glucagon receptor agonists of a similar type 1 peptide in the treatment of carbohydrate metabolism disorders in patients with hypercortisolism acromegaly.

Subjective symptoms: changes in facial features or body shape, muscle weakness and poor exercise tolerance, a tendency of the skin to traumatize - difficult healing ulcers, a tendency to hematomas; polydipsia and polyuria (→ it is necessary to control glycemia; in severe cases, hyperosmolar hyperglycemic syndrome may develop); increased appetite; headache and dizziness (→ blood pressure should be monitored); emotional lability, tendency to depression, memory impairment, rarely psychotic states; bone pain (in case of osteoporosis → pathological fractures of the vertebral bodies, ribs, pubic and ischial bones should be looked for); tendency to infections, especially opportunistic (eg fungal), often with a severe course, as well as tuberculosis; symptoms of coronary heart disease (→ perform lipid profile control), heart failure or venous thrombosis and thromboembolism (prothrombotic

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action of GCS), symptoms of gastric ulcer and duodenal ulcer (especially in patients taking NSAIDs); symptoms of urolithiasis (due to hypercalciuria and hyperphosphaturia); decreased potency in men, scanty menstruation or secondary amenorrhea in women.

In recent years, close attention has been focused on the study of the physiology of incretin hormones (hormones of the gastrointestinal tract involved in the regulation of glucose metabolism) and their secretion under conditions of various disorders of carbohydrate metabolism. A detailed study of the incretin system in patients with "secondary" diabetes mellitus, including in patients with neuroendocrine diseases, has not been carried out. Determination of the features of the secretion of incretin hormones in conditions of excess cortisol and growth hormone / insulin growth factor-1 can determine the place of incretin-targeted therapy - type 4 dipeptidyl peptidase inhibitors and type 1 glucagon-like peptide receptor agonists in the treatment of carbohydrate metabolism disorders in patients with hypercorticorticoidism ...

Objective symptoms: obesity of the central type, with fat deposition on the trunk and neck ("bull's neck"), with the presence of fat pads in the supraclavicular fossa and with thin limbs; the face is rounded ("moon face"), often reddened (due to hyperemia and thinning of the skin), with dilated vessels; short thick neck; atrophy of the muscles of the limbs and trunk; wide, red or red-blue stretch marks on the skin of the abdomen, thighs, mammary glands, and in young people - also around the axillary, elbow and popliteal fossae (→ should be differentiated from narrow, pink, multiple stretch marks of the skin that occur in young people during the period rapid weight gain and fade over time); thinning of the skin, easily occurring hemorrhages in the skin, sometimes spontaneous petechiae; symptoms of hyperandrogenization of varying severity - acne and hirsutism (→ differential diagnosis with polycystic ovary syndrome should be performed); arterial hypertension (in most patients, mostly mild or moderate), skin hyperpigmentation (in patients with a long-term high concentration of ACTH); swelling in the lower extremities.

Natural course: with subclinical KS, even long-term, the development of a characteristic complex of symptoms may not occur; The risk of progression to severe KS is low; therefore, subclinical KS should not be considered an early phase of KS from the outset. Deployed KS is diagnosed only at the late stage of a long-term illness. Much more often, only some of the symptoms are present, for example. impaired glucose tolerance or diabetes mellitus, dyslipidemia, arterial hypertension and rapid weight gain (obesity), constituting a picture of metabolic syndrome; the risk of osteoporosis is also increased.

Carbohydrates in the human body are present in a much smaller amount (no more than 2% of dry body weight) than proteins and lipids. In the body, carbohydrates perform a variety of functions, the most important of which are energy (the main source of energy for cells) and structural (an essential component of most intracellular structures).

In addition, carbohydrates are used for the synthesis of nucleic acids (ribose, deoxyribose), and also form compounds with protein (glycoproteins, proteoglycans), lipids (glycolipids) and other substances (heteromonosaccharides), being components of many enzymes and regulatory systems that provide numerous specific functions . Chemically, carbohydrates are aldehydes and ketones of polyhydric alcohols. Monosaccharides combine through a glycosidic bond, forming disaccharides, oligosaccharides (3 to 6 monosaccharide residues) and polysaccharides (glycogen, starch). The most common in the body are pentoses (included in nucleic acids and many coenzymes, in particular NADP) and hexose (glucose, fructose, galactose).

For energy metabolism, glucose is of the greatest importance. Firstly, it is the only source of energy for the central nervous system, in which there are no energy reserves, and it does not use other sources of energy, for example, proteins and fats (with the exception of ketone bodies during starvation). Secondly, the body creates a reserve of glucose in the form of glycogen, which is quickly broken down and supplies glucose to the blood.

Thirdly, for the complete oxidation of 1 glucose molecule (to CO2 and H2O, which are easily removed from the body), less oxygen is required than for the oxidation of a fatty acid, and the yield of macroergs is significant: 38 ATP molecules. In the metabolism of carbohydrates, it is customary to distinguish the following stages: - digestion and absorption of carbohydrates in the gastrointestinal tract; - processes of synthesis and cleavage of glycogen; - intermediate metabolism of carbohydrates and their utilization in tissues. Causal factors that disrupt carbohydrate metabolism can manifest themselves at each of these stages of carbohydrate metabolism.

RESULTS AND DISCUSSIONS

Itsenko-Cushing's disease and type 2 diabetes sometimes have a similar clinical picture, which complicates the timely diagnosis of endogenous

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hypercortisolism. The presence of disorders of carbohydrate metabolism, especially in combination with other manifestations of this neuroendocrine disease, such as dysplastic obesity, poorly controlled arterial hypertension, dictates the need to exclude its secondary nature. Corticosteroids alter the amount and distribution of body fat. Excess fat is deposited all over the torso and can be especially noticeable in the upper back (sometimes referred to as the bison hump). Patients with Cushing's syndrome have a large, round face (moon face). The arms and legs usually remain thin compared to the rest of the massive torso.

Muscles lose their mass, which leads to muscle weakness. The skin becomes thin, bruises and wounds easily appear on it, which do not heal well. Purple streaks similar to stretch marks (striae) may appear on the belly and chest. Patients with Cushing's syndrome tend to tire quickly.

Prolonged increases in corticosteroid levels lead to high blood pressure (hypertension), weakening of the bones (osteoporosis), and a decrease in the body's resistance to infection. The risk of developing kidney stones and diabetes mellitus increases, and mental disorders, including depression and hallucinations, may develop.

TREATMENT FOR CUSHING'S SYNDROME

- A diet high in protein and taking potassium supplements (or potassium-sparing medications such as spironolactone)
- Adrenal inhibitors, such as metyrapone or ketoconazole, and less commonly mitotane
- Surgery or radiation therapy for pituitary, adrenal, or ectopic ACHT-producing tumors
- Sometimes somatostatin analogs, dopamine agonists, or glucocorticoid receptor antagonist mifepristone

First of all, it is necessary to maintain the general condition of the patient with a diet high in protein and a sufficient amount of potassium. In severe clinical manifestations, it becomes necessary to block the secretion of corticosteroids, for which metirapone (not registered in the Russian Federation) is prescribed at 250 mg -1 g orally 3 times a day or ketoconazole 400 mg orally once a day (maximum 400 mg 3 times a day) ... Most likely, the action of ketoconazole is slower and sometimes hepatotoxic. Parenteral etomidate (an intravenous anesthetic that also blocks the production of cortisol) may be life-saving for patients with transient symptoms; given as an intravenous infusion: the starting dose is usually 1 to 2 mg / hr, increasing as needed, with frequent assessments of cortisol levels and appropriate titration doses.

ACTH-producing pituitary tumors must be surgically removed or destroyed with radiation therapy. If the tumor is not visualized, but there are good reasons to believe that the pituitary gland is the source of excess ACTH, an attempt is made to total hypophysectomy, especially in elderly patients. In younger patients, high-intensity irradiation of the pituitary gland with a dose of 45 Gy (Gray) can be used. However, in children, irradiation of the pituitary gland can reduce the secretion of growth hormone and sometimes cause precocious puberty.

In specialized centers, a single irradiation with a proton beam, which ensures absorption by the pituitary gland of 100 Gy, is successfully used, or radiosurgery is used. Alternatively, proton therapy can be used if available. The reaction to radiation sometimes appears after several years; in children, the effect is faster.

Studies show that mild cases of persistent or recurrent disease are amenable to therapy with a somatostatin analogue, pasireotide. However, hyperglycemia is a significant adverse reaction. Occasionally, the dopamine agonist cabergoline can also be used . An alternative approach is to use the corticosteroid receptor blocker mifepristone. The glucose receptor antagonist mifepristone increases serum cortisol but blocks the effects of corticosteroids and may cause hypokalemia.

In cases where radiotherapy is contraindicated, as well as in the absence of the effect of surgery, irradiation or examination of the pituitary gland (with possible adenomectomy), bilateral adrenalectomy is performed in patients with pituitary hypercorticism. After such an operation, lifelong corticosteroid replacement therapy is required.

Tumors of the adrenal cortex are removed surgically. During and after the operation, the patient needs to be injected with hydrocortisone, since the non-tumor tissue of the cortex atrophies and does not function during the illness. For benign adenomas, laparoscopic surgery can be performed. Multinodular adrenal hyperplasia may require bilateral adrenalectomy. Even with (presumably) total adrenalectomy, functional relapse occurs in some patients.

With ectopic ACTH syndrome, the non-pituitary tumor producing ACTH is removed. However, in some cases, the tumor is disseminated and cannot be removed. Severe metabolic disturbances (eg, hypokalemia) are usually controlled with adrenal hormone inhibitors such as metirapone 500 mg orally

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3 times a day (or more, up to a maximum daily dose of 6 g / day) or mitotane 0.5 g 1 time per day (maximum 3-4 g / day). When using mitotane, it becomes necessary to take large doses of hydrocortisone or dexamethasone, sometimes making the measurement of cortisol production unreliable. Hypercholesterolemia may also develop. Ketoconazole (in doses of 400-1200 mg orally once a day) also blocks the synthesis of corticosteroids, but this drug has hepatotoxicity, and its use may be accompanied by manifestations of Addison's disease. Mifepristone may also be useful in the treatment of ectopic ACTH production syndrome; however, because it blocks the action of cortisol but does not lower serum levels, monitoring its use can be problematic. In an emergency, parenteral administration of etomidate can cause a rapid decrease in serum cortisol levels, therefore its use requires careful monitoring of the patient's condition.

Occasionally, ACTH-secreting tumors respond to long-acting somatostatin analogs (eg, octreotide and / or others), but their use for> 2 years requires close clinical monitoring of patients, as complications such as mild gastritis, cholelithiasis may develop , cholangitis, as well as melabsorption.

In women, the menstrual cycle is usually irregular. In some patients, the adrenal glands also synthesize large amounts of male sex hormones (testosterone and similar hormones), which leads to increased facial and body hair growth and baldness in women.

CONCLUSION

In turn, the achievement of a satisfactory postoperative result in relation to corticotropinoma does not always lead to a regression of the complications that have formed. The lack of normalization of glycemic parameters, lipid metabolism, and blood pressure puts patients at high risk for the development of cardiovascular complications in the future and dictates the need for careful dynamic monitoring by specialists. To achieve diabetes compensation in comorbid patients, it is worth considering therapy with new-generation drugs (dipeptidyl peptidase-4 inhibitors, sodium glucose co-transporter type 2 inhibitors), if necessary in combination with other drugs.

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