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Clinical Observation of Iatrogenic Itsenko-Cushing's Syndrome at Patient with Bronchial Asthma

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Abstract

American physician Philip Hench, who first used glucocorticosteroids (GCS) to treat patients with rheumatoid arthritis, underwent a revolution in medicine and was awarded the Nobel Prize in 1950 for his work. Since then almost all have become known about the GCS. Doctors working with the GCS often respond about such therapy as walking on the razor's edge. Alas, there are clinical situations when it is impossible to avoid high doses of these drugs, in other cases there are always trade-offs. The appointment of GCS should be preceded by an in-depth analysis of the need and justification of the choice of such therapy, because sometimes the severity of side effects and complications after treatment with GCS exceeds the severity of the initial disease. In this article, we present our own clinical observation of a patient with iatrogenic Itsenko-Cushing syndrome, which resulted from a long illicit therapy with prednisolone.

Keywords: clinical observation, iatrogenic Itsenko-Cushing's syndrome, bronchial asthma, prednisolone, glucocorticosteroids, diabetes mellitus.

1. Introduction

According to world statistics, about 1 % of the population uses long-term systemic corticosteroids. Among them, 2/3 manifests Itsenko-Cushing's drug syndrome (Fardet *et al.*, 2011; Venkateshwarlu Nandyala *et al.*, 2017). Sometimes the treatment of GCS is justified, and it is impossible to replace the drug. In such cases, it is usually a question of correcting (minimizing) the side effects of taking them, selecting the minimum effective doses and the most effective drug in a particular clinical situation (Saurabh Srivastava *et al.*, 2015; Tiwari *et al.*, 2013). The most notable achievement of the mid-twentieth century can be considered the discovery of topical GCS, which marked the beginning of a new era of highly effective therapy with minimal systemic effects (O'Sobande, Kerckmar, 2008). However, in some situations, doctors forget about the possibility of revising the therapy with the advent of new modern alternatives, which is often due to the fact that the drug used "in the old way" continues to have a therapeutic effect.

Taking a physiological dose of 2.5 to 7.5 mg of prednisolone per day is usually not accompanied by side effects (Fardet *et al.*, 2011). The use of the drug in higher doses (more than 7.5 mg per day) can lead to functional insufficiency of the adrenal cortex and the development of complications (Borisova, 2004). Acceptance of systemic corticosteroids for more than 4–5 months can lead to atrophy of the adrenal cortex in 40 % of patients (Fardet *et al.*, 2011).

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2. Clinical case

We present a clinical observation of patient S. 55 years old hospitalized in the Department of Endocrinology of Saratov Regional Clinical Hospital (RCH) in October 2017. Complaints at the time of hospitalization: numbness, burning, coldness of the feet; pain in the muscles of the legs, worse when walking; increase in blood pressure (BP) to 200 and 110 mmHg.; pain of pressing nature behind the sternum with moderate exertion; shortness of breath of a mixed character with little exertion; cardiopalmus; memory loss; pain in the thoracic, lumbar spine and knee joints; frequent urination up to 7-8 times a day.

From the anamnesis data: at 28 years (1990) after giving birth, she began to notice frequent bronchitis (2-3 times a year), including in the summer months. She received the treatment by herself, usually it were chest fees, herbal remedies, however, due to the appearance of dyspnea attacks, whistling in the chest, she consulted a district physician at the place of residence (city of the Saratov region), who diagnosed bronchial asthma (BA) and prescribed treatment: regular intake of prednisone (per os) 30 mg per day. When the patient's condition deteriorated, she received inpatient treatment at the Department of Therapy of the District Hospital (DH), where, according to her, received treatment in the form of drip prednisone up to 150 mg per day for 7 to 10 days with a positive effect. With the course of the disease, the patient became allergic to a number of substances (house dust, pollen from a number of plants, aspirin). In the early 2000s she consulted at the allergic center of Saratov (she does not remember the results). Over the past 10 years, prednisolone was taken daily at a dose of 10 mg for asthma, while salbutamol was used during asthma attack. Attacks of dyspnea are practically not observed during the last few years. Until this hospitalization in the RCH patient S. have not received any consultation oa pulmonologist. Since 1992, she has noticed an increase in body weight (initial body weight 44 kg, currently weighing 102 kg). Since 2004, she began to notice general weakness, dryness in the vagina, burning, itching of the genitals. During the examination in the DH: blood glucose 15 mmol/l, in the general analysis of urine - glycosuria. Endocrinologist of the DH for the first time diagnosed diabetes mellitus (DM). Oral glucose-lowering therapy was prescribed (siofor, diabeton, the doses of the drugs changed, it cannot specify the specific ones). In 2009, she stumbled at home. It was diagnosed with a fracture of the tibia and tibia of the bones on the right. Since 2010, an increase in blood pressure to 200 and 110 mmHg. Treatment is prescribed by a physician of the DH: indapamide 2.5 mg per day, enalapril 20 mg per day which is currently also received. Against the background of therapy, blood pressure is 150-160 and 90 mmHg. Statins do not accept. Since 2014, she noted a decrease in vision. Since 2015, she noticed deterioration in memory and attention (she cannot remember a single drug, which she receives daily). In 2016, with a random fall of the house, a fracture of the right brachial bone was occurred. In 2016, due to unsatisfactory carbohydrate metabolism rates, she was hospitalized at one of Saratov Clinical Hospitals, where during the examination there were revealed complications of diabetes (fatty hepatitis, polyneuropathy, lower extremity macroangiopathy, retinopathy, nephropathy). Transferred to insulin therapy. In October 2017, due to prolonged decompensation of carbohydrate metabolism (glycaemia up to 18 mmol/l), progression of painful, convulsive lower extremity syndromes, was hospitalized at the Department of Endocrinology in the RCH for examination and correction of the therapy being conducted. Heredity on endocrine pathology is burdened by: mother, sister and father – type 2 diabetes; uncle – type 1 DM. Smoking and taking drugs denies. Alcohol does not abuse.

Physical examination (see [Figure 1](#)): the state is relatively satisfactory. The skin has tanning shade. On the skin of forearms, face, lower legs – xanthomas. Subcutaneous tissue is excessively developed, unevenly distributed, mainly in the upper half of the body. "Buffalo" body type. BMI 43 kg/m², waist 139 cm. Lower limbs: edema traces of the legs, dry skin, and atrophic, partial lack of hair growth, plantar hyperkeratosis, onychomycosis, and hyperpigmentation of the legs skin after trophic ulcers. The pulsation of the arteries dorsalis pedis, tibialis posterior is weakened to the right and left. Tactile sensitivity is reduced by the type of golf, mostly on the right. Varicose veins of the lower extremities: on both sides. Apical impulse is not palpable. Muffled heart sounds, rhythmic, heart rate 120 per minute. Blood pressure 140 and 90 mm Hg. Breathing is hard (inhale: exhale = 1: 1), wheezing is not heard. In the Romberg position is unstable. The most significant results of laboratory and instrumental studies and the conclusions of specialists – consultants are presented in [Table 1](#).



Fig. 1. External examination of patient S., 55 years

Table 1. The results of laboratory and instrumental investigation of patient S. 55 years

Glycemia to 14.5 mmol/l at admission, further to 7.2 mmol/l in the glycemc profile. HbA1c 6,5 %	Cholesterol 6.5 mmol/l, LDL 4.2 mmol/l, Atherogenic index 3.8	WBC $12.31 \cdot 10^{12} /l$
Na⁺ 134,9 mmol/l (Norm: 135-148) K⁺ 4,55 mmol /l (Norm: 3,5-5,3) Ca²⁺ 1,14 mmol/l (Norm:1,13-1,32)	Creatinine 79 μ mol/l GFR 73 ml/min.	C- reactive protein 2.91 mg/ml (Norm: 0.78-1.89)
General urine analysis: light yellow transparent Leukocytes 4-6 in sight. Albumin 10 mg/l Albumin / Creatinine N	Daily proteinuria Protein 0.03 g	Parathormone 25 pg/ml (Norm: 9.5-75)
Oculist: Diabetic retinopathy.	ECG: Sinus rhythm with heart rate 66 per minute. The horizontal position of the electrical axis of the heart. Reducing the voltage of the R wave in the chest leads.	
EGD: Chronic focal atrophic gastroduodenitis.		
Ultrasound of the kidneys: cyst of the left kidney.	Transthoracic echocardiography: Nonspecific degenerative changes in the walls of the aorta, aortic,	

Abdominal ultrasound: Diffuse changes in the liver and pancreas. Deformation of the gallbladder. Hypertrophic cholecystitis.	mitral, tricuspid valves. Aortic regurgitation is mild. Concentric hypertrophy of the left ventricular myocardium (LV). LV diastolic function is impaired by the relaxation type. Small to moderate mitral regurgitation. From small to moderate tricuspid regurgitation. Small pulmonary hypertension.
Neurologist: Diabetic distal symmetric sensorimotor polyneuropathy of the lower extremities. Chronic cerebral ischemia of complex genesis.	Spirography: respiratory function is impaired due to moderate obstruction. The test with a bronchodilator is positive: the increase in forced expiratory volume is 23% of the initial value.

The patient was diagnosed with: Primary: Diabetes mellitus with GCS, the target level of glycated hemoglobin is <7.0 %. Diabetic retinopathy, diabetic angiopathy of the lower extremities, diabetes-hypertensive nephropathy. Arterial hypertension stage 3, risk IV. CHD: Angina of exertion II FC. Chronic cerebral ischemia. Atherosclerosis of the aorta, cerebral arteries. Secondary osteoporosis in patients receiving GCS at the fracture stage. Background: Itsenko-Cushing's Drug Syndrome. Bronchial asthma, mixed genesis, medium-severe persistent course, remission phase. Companion: Exogenous-constitutional obesity grade III, abdominal form. Varicose disease of the lower extremities. Complications: Insufficiency of blood circulation stage I (III FC on the NYHA). Chronic venous insufficiency of the lower extremities.

The patient was hospitalized to correct the ongoing hypoglycemic therapy of DM and change the therapy of systemic corticosteroids into modern topical preparations for the treatment of asthma.

3. Discussion

The Global Initiative for Asthma (GINA) has become widely known to the Russian medical community since 1995. It was in 1995 that the international concept of managing patients with this disease appeared. The GINA recommendations spelled out a stepwise approach to the treatment of asthma depending on the severity of clinical manifestations. Moreover, the scope of application of systemic corticosteroids already in 1995 was limited to the phases of moderate and severe exacerbations (GINA,1995). For 27 years, the patient S. was treated with systemic GCS, while she was never consulted by a pulmonologist and therapy in favor of inhaled GCS was not reviewed. In addition, the patient did not receive drugs to correct the side effects of the ongoing systemic GCS therapy. Long-term therapy with prednisone in this clinical case contributed to the stabilization of asthma, the severity of which did not require such an approach to therapy, and led to the development of Cushing's drug syndrome and multiple organ complications, in most cases that are irreversible and progressive. According to the latest revision of GINA 2018, the treatment of BA with systemic steroids is carried out only in case of exacerbations (moderate and severe) up to 7 days in a daily dose of 40-50 mg with subsequent cancellation. Cancellation of systemic corticosteroids is carried out only against the background of the appointment of inhaled corticosteroids. In addition to the insulin therapy scheme and cardiotropic therapy (losartan 50 mg per day + amlodipine 10 mg per day + torasemide 5 mg per day + spironolactone 50 mg per day; atorvastatin 40 mg per day, cardiomagnyl 150 mg per day, nitrates – on demand – for pain in the heart) reducing prednisone 1/4 tablets per week until completely discontinued while using inhalation topical preparations (GINA, 2018): beclomethasone 250 mcg 2 inhalations 2 times a day (or budesonide 400 mcg 2 times a day) + formoterol 12 mcg in 1 inhalation 1 time per day with the appearance of asthma attack during the day or 1 inhalation at night with night asthma attacks and symptomatic use of salbutamol in case of necessity.

4. Conclusion

In 2018, the Russian healthcare system has a stormy discussion about the universal implementation of clinical guidelines in medical practice. Unfortunately, no final decision has yet been received. Obviously, the management of the patient with bronchial asthma did not comply with the clinical recommendations and led to the development of severe consequences of incorrect therapy - the Cushing syndrome and its complications. It would not be hard from the point of view

of moral ethics to discuss the actions of colleagues, but in this situation it is more about a violation of the most important postulate of the doctor in relation to the patient – “do no harm”. In conclusion, the authors would like to cite the words of the ancient East healer Avicenna, which are very relevant in described clinical situation: “There are no hopeless patients. There are only hopeless doctors.”

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