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Long-diagnosed primary adrenal insufficiency in the setting of Werlhof's disease. A clinical case report

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Abstract. *Chronic adrenal insufficiency is an endocrine disease caused by insufficient secretion of adrenal hormones due to dysfunction of one or more links of the hypothalamic-pituitary-adrenal axis. The highest prevalence has been documented in Scandinavian countries: 15–22 people per 100,000 population, while other European countries report 10 cases per 100,000 population. Autoimmune adrenalitis is the most common cause of primary adrenal insufficiency in adults, and it can be either alone (40 %) or a component of autoimmune polyglandular syndromes (60 %). The etiologic factors of primary adrenal insufficiency include tuberculosis or AIDS. These causes of adrenal cortical insufficiency are particularly relevant in Ukraine. The article describes a clinical case of a patient with both primary adrenal insufficiency and Werlhof's disease. The prevalence of adrenal insufficiency and etiologic factors of primary adrenal insufficiency are highlighted. A detailed differential diagnosis of primary adrenal insufficiency with other diseases that could cause clinical symptoms such as hypoglycemic states, severe weight loss, hypotension, severe muscle weakness, hyponatremia, hyperkalemia is performed. The basic principles of diagnosis, treatment, and prognosis in primary adrenal insufficiency are discussed. Despite typical, specific manifestations of adrenal insufficiency, diagnosis in real clinical practice is difficult. Awareness and vigilance of doctors regarding the symptoms of adrenal insufficiency is necessary. Late detection of chronic adrenal insufficiency can lead to complications. Timely diagnosis and treatment of chronic adrenal insufficiency improves disease prognosis and quality of life.*
Keywords: *adrenal insufficiency; insulinoma; hypoglycemia; hyponatremia; hypochloraemia; hypotension; autoimmune thrombocytopenia; chromogranin A*

Introduction

Chronic adrenal insufficiency is an endocrine disease caused by insufficient secretion of adrenal cortex hormones due to dysfunction of one or more links of the hypothalamic-pituitary-adrenal system [1]. The highest prevalence has been documented in Scandinavian countries: 15–22 people per 100,000 population, while other European countries report 10 cases per 100,000 population [2, 3].

Autoimmune adrenalitis is the most common cause (up to 90% of cases) of primary adrenal insufficiency in adults [4]. It can be either isolated (40 %) or a component of autoimmune polyglandular syndromes (60 %) [5, 6]. It is also necessary to point out such etiologic factors of primary adrenal insufficiency as tuberculosis and AIDS [7]. These causes of adrenal cortical insufficiency are especially relevant in Ukraine.

Against the backdrop of the COVID-19 pandemic, cases of primary adrenal insufficiency of autoimmune genesis have become more frequent. In this case, there are both disorders of adrenocorticotropic hormone (ACTH) synthesis (SARS-CoV-2 RNA was detected in the hypothalamus during autopsies of patients who died as a result of COVID-19), with the subsequent development of adrenal insufficiency, and changes in the adrenal glands themselves (degeneration and necrosis of cortical cells, small vein vasculitis, autoimmune reactions with monocytic and lymphocytic infiltration) [8].

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Despite the typical, specific manifestations of chronic kidney disease, diagnosis in actual clinical practice is difficult. Patients can be treated for a long time by general practitioners of family medicine, cardiologists, gastroenterologists, hematologists and other specialists [9].

It should be emphasized that timely detection of adrenal cortex insufficiency and adequate replacement therapy provide patients with a proper quality of life, as was the case in the clinical case described below.

Clinical case

Patient K., 23 years old, was admitted to the surgical department with suspected insulinoma with complaints of abdominal heaviness, nausea, intermittent vomiting, general weakness, loss of appetite, pain in the lower extremities, darkening of the eyes, a tendency to hypotension, and frequent hypoglycemic states.

Medical history: according to the patient, he had been feeling sick since January 2019, when he developed abdominal pain. Initially, the condition was assessed as food poisoning. On 02/16/2019, he was hospitalized in the intensive care unit of the Regional Clinical Hospital of Ivano-Frankivsk Regional Council (RCH), where he was diagnosed with hemorrhagic gastritis. He was discharged on February 20, 2019 with improvement. The abdominal pain worsened again at the end of February, so on 03/01/2019 the patient was operated on at Bohorodchany Central District Hospital (diagnostic laparoscopy). An enlarged lymph node from the abdominal cavity was taken for histological examination. Histological and immunohistochemical examination of the lymph node: paracortical hyperplasia. On 03/07/2019, the patient's condition deteriorated sharply, hyperthermia and hypotension developed, so he was re-hospitalized in the intensive care unit of the RCH in an extremely serious condition. According to a computed tomography (CT) scan dated 03/07/2019, lymphadenopathy and signs of splenic abscess were found. The level of procalcitonin in the blood was 1.24 mg/ml (normally 0.1 mg/ml), and during the repeated test on the same day 0.19 mg/ml. Antimicrobial agents for systemic use (meropenem, glycopeptide antibiotics), antibacterial agents for systemic use (imidazole derivatives), antifungal agents for systemic use (triazole derivatives), and detoxification therapy were prescribed. The repeated CT scan on 03/21/2019 showed positive dynamics.

The patient was further examined in the nephrology department of the RCH. According to the discharge report, a viral infection (cytomegalovirus, EBV, HCV, HIV) was excluded, and no changes in the lungs were detected. A repeated CT scan of the abdominal cavity on 03/21/2019 diagnosed moderate splenomegaly, lymphadenopathy. He was discharged in satisfactory condition. From the beginning of May 2019, the general condition deteriorated again, with severe general weakness, decreased blood pressure (BP) to 60/40 mm Hg and body weight (since January 2019, the patient lost 16 kg). The patient was referred to the Intensive Care Center for Sepsis in Kyiv, but after a consultation on 05/24/2019, septic status was excluded. Treatment was continued at the National Scientific Center M.D. Strazhesko Institute of Cardiology of the NAMS of Ukraine. Magnetic resonance imaging (MRI) revealed no organic changes in the heart and brain. According to the data of daily ECG monitoring, a labile sinus rhythm with periods of sinus arrhythmia was established. During inpatient treatment, the patient had an increase in leukocyte count from 8.1×10^9/L to 22.35×10^9/L with a simultaneous decrease in platelet count from 150×10^{12}/L to 11×10^{12}/L.

Due to thrombocytopenia, the patient was hospitalized in the hematology department of the Institute of Blood Pathology and Transfusion Therapy of the NAMS of Ukraine, where he was prescribed steroid hormone drugs. After the prescribed therapy, the platelet count returned to normal levels. In November 2019, the patient was prescribed an antihemorrhagic drug (systemic hemostatic agent, eltrombopag in a dose of 50 mg), a bone marrow puncture was performed, and immune thrombocytopenia was diagnosed. In January-February 2020, the platelet count did not exceed $20–30 \times 10^{12}$/L, and there were episodes of gum bleeding. Due to the ineffectiveness of previous therapy, an antineoplastic agent (monoclonal antibodies, rituximab) was prescribed. At the same time, hypotension persisted and hypoglycemic states continued. At the same time, the patient's condition improved with the administration of glucocorticoids. Subsequently, the patient was hospitalized in the hematology department of the Ivano-Frankivsk Regional Clinical Hospital, received 4 courses of rituximab treatment, platelet count was $125–164 \times 10^{12}$/L, without hemorrhagic syndrome.

The general condition deteriorated sharply on 08/21/2023, so the patient was hospitalized in the hematology department of the RCH with a diagnosis: idiopathic thrombocytopenic purpura, severe form, continuously recurrent course. Treatment brought improvement in the general condition.

On an outpatient basis, the patient underwent an MRI of the abdominal cavity. MRI results (04.09.2023): signs of a volumetric formation of the isthmus of the pancreas, which is more consistent with a neuroendocrine tumor of the pancreas, probably with low metabolic activity, insulinoma is possible.

On 09/06/2023, the patient was hospitalized in the surgical department of the RCH for further diagnosis and treatment. Objectively: reduced body fatness (BMI 16.4 kg/m^2), blood pressure 70/40 mm Hg, pale skin, no hyperpigmentation in the skin folds, no palm discoloration. Biochemical blood test: total protein 73.6 g/L; alpha-amylase 45.0 U/L (reference values 20–104 U/L); serum glucose 5.65 mmol/L (reference values 4.2–6.4 mmol/L); potassium 3.88 mmol/L (reference values 3.44–5.3 mmol/L) sodium 103.1 mmol/L (reference values 130.5–156.6 mmol/L); chlorides 90.1 mmol/L (reference values 95–110 mmol/L); urea 9.7 mmol/L; creatinine 107.2 μmol/L (reference values 61.9–106.1 μmol/L). Glycemic profile: 4.56–2.91–3.4–4.44 mmol/L. Blood test from 08/31/2023: immunoreactive insulin 3.52 μIU/ml (reference values 2.6–24.9 μIU/ml); C-peptide 0.961 ng/ml (reference values 0.9–7.1 ng/ml); tumor markers of the pancreas, gallbladder (CA-19-9), serum 11.75 U/ml (reference values < 34.0 U/ml); cancer embryonic antigen (CEA), serum 0.752 ng/ml (reference values < 3.4). The patient was consulted by an endocrinologist in the surgical department. Taking into account the patient's complaints of severe weakness, nausea, vomiting, weight

loss, hypotension (with a retrospective assessment of medical history in Ukrainian clinics), a tendency to hypoglycemia, hyponatremia, hypochloraemia, normal levels of immunoreactive insulin, and C-peptide, no hyperpigmentation of the skin, the presence of a volumetric formation of the pancreatic isthmus, a preliminary diagnosis was made: secondary adrenal insufficiency (hypothalamic-pituitary), and a bulky hormonally inactive pancreatic mass. In order to confirm the diagnosis, the patient was prescribed to determine the level of ACTH and cortisol, chromogranin A and MRI of the pituitary gland with contrast.

According to MRI data of 09/08/23, foci of signal loss in SWI mode in the subcortical white matter are probably manifestations of cerebral angiopathy. Results of blood test from 09/07/2023: ACTH 726 ng/ml (reference values < 46 ng/ml); blood cortisol < 1.0 mcg/dL (reference values, morning 7.00–10.00, 5–25 mcg/dL); chromogranin A 52.69 mcg/L (reference values < 100 mcg/L). The diagnosis was made: primary adrenal insufficiency in the state of decompensation. Idiopathic thrombocytopenic purpura, severe form, continuously recurrent course. Volumetric pancreatic mass, hormonally inactive.

Discussion

In assessing the patient's condition, we made a differential diagnosis between primary and secondary adrenal insufficiency, as well as with diseases characterized by hyperpigmentation, arterial hypotension, hypoglycemia, and gastrointestinal disorders. In secondary pituitary gland insufficiency, unlike primary gland insufficiency, pallor of the skin, decreased ACTH levels in the blood plasma with possible loss of function of other tropic hormones and signs of other endocrine gland insufficiency (hypothyroidism, hypogonadism, and growth failure) are observed. In contrast to pituitary insufficiency, in polyglandular insufficiency of autoimmune origin, organ-specific autoantibodies are detected in the blood of patients. With hypotension of another genesis, the differential diagnosis is not difficult and is carried out using hormonal laboratory tests.

Anorexia and gastrointestinal disorders occur in diseases of the digestive system, pregnancy, nephritis, and neurasthenia. A decrease in body weight is always observed in chronic AC insufficiency, so in the differential diagnosis it is also necessary to take into account diseases accompanied by weight loss: chronic infections (tuberculosis), malabsorption syndrome, malignant neoplasms, and leukemia. In these cases, the blood glucocorticoid level is normal or slightly decreased, but the response to ACTH stimulation is unchanged.

It is also necessary to carry out a differential diagnosis in the described case with insulinoma, since the patient had frequent hypoglycemic states, and a CT scan of the abdominal cavity revealed a mass in the area of the pancreatic isthmus. The causes of hypoglycemia in adrenal insufficiency are associated with the destruction of the tissue of the adrenal glands themselves.

Hypoglycemic states in patients with chronic adrenal insufficiency can occur both on an empty stomach and 2–3 hours after a carbohydrate-rich meal. Attacks are accompanied by weakness, hunger, and sweating. Hypoglycemia develops as a result of decreased cortisol secretion, decreased gluconeogenesis, and glycogen stores in the liver. Insulinoma is characterized by hypoglycemic attacks associated with constant insulin release, independent of blood glucose level. Frequent attacks of hypoglycemia cause damage to the central nervous system. In some patients, they resemble an epileptic seizure, which leads to hospitalization in a neurological department. Hypoglycemic attacks are interrupted by eating, so patients constantly consume a large amount of food, mainly carbohydrates, what contributes to the development of obesity. And in our case, the patient had a sharp weight loss, lack of appetite, nausea, and vomiting.

The diagnosis of insulinoma is based on the detection of the classic and pathognomonic Whipple triad: neuropsychiatric manifestations during fasting; blood glucose is less than 2.78 mmol/L; elimination of the attack by oral or intravenous administration of glucose solution, as well as a clinical picture typical of hypoglycemia. The "gold standard" at the first stage of diagnosis of hypoglycemic syndrome and confirmation of endogenous hyperinsulinism is a fasting test [10]. In the case described, the patient was not subjected to a fasting test, as he had been restricted in food intake for a long time due to severe nausea and vomiting, and no distinct episodes of hypoglycemia were observed.

In our observation, the verification of the diagnosis was based on a retrospective assessment of the medical history in Ukrainian clinics, the patient's tendency to hypotension, hypoglycemia (blood glucose from 2.9 to 8.8 mmol/L), hyponatremia, and hypochloraemia throughout the entire time. In order to make a differential diagnosis between primary and secondary adrenal insufficiency, as well as between adrenal insufficiency and insulinoma, the patient was prescribed to determine the insulin level, C-peptide, ACTH and cortisol, chromogranin A and MRI of the pituitary gland.

The patient was recommended a high-calorie diet consisting of a sufficient amount of proteins, increased amounts of table salt (8–10 g per day), and vitamins, especially ascorbic acid. The patient was prescribed hormone replacement therapy with hydrocortisone at a dose of 10 mg twice a day with transfer to the department for endocrinology.

During the hospital stay, the patient's general condition improved, nausea and vomiting disappeared, weight increased by 4 kg, appetite increased, and muscle weakness in the lower extremities decreased. The patient was discharged from the hospital on hormone replacement therapy under the supervision of an endocrinologist and hematologist.

Conclusions

Despite the typical, specific manifestations of adrenal insufficiency, diagnosis in actual clinical practice is difficult. Awareness and alertness of general practitioners of family medicine, cardiologists, gastroenterologists, hematologists, and surgeons regarding the symptoms of adrenal insufficiency is necessary. Delayed detection of chronic adrenal insufficiency can lead to complications and an increased risk of mortality. Differential diagnosis of chronic adrenal insufficiency should be carried out between diseases characterized by hyperpigmentation, arterial hypotension, hypoglycemia, and gastrointestinal disorders. Timely diagnosis and treatment of chronic adrenal insufficiency improves the prognosis of the disease and quality of life.

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Тривало недіагностована первинна надниркова недостатність на фоні хвороби Верльгофа. Клінічний випадок

Резюме. Хронічна надниркова недостатність — ендокринне захворювання, обумовлене недостатньою секрецією гормонів кори надниркових залоз унаслідок порушення функціонування однієї або декількох ланок гіпоталамо-гіпофізарно-надниркової системи. Найвища поширеність задокументована в скандинавських країнах — 15–22 особи на 100 000 населення, тоді як інші європейські країни повідомляють про 10 випадків на 100 000 населення. Автоімунний адреналіт є найпоширенішою причиною первинної надниркової недостатності в дорослих, він може бути як ізольованим (40 %), так і компонентом автоімунних полігландулярних синдромів (60 %). До етіологічних факторів первинної надниркової недостатності відносять і туберкульозний процес або СНІД. Ці причини виникнення недостатності кори надниркових залоз особливо актуальні в Україні. У статті описано клінічний випадок первинної надниркової недостатності та хвороби Верльгофа. Висвітлено поширеність надниркової недостатності, етіологічні фактори первинної недостатності надниркових залоз. Проведено детальну диференційну діагностику первинної надниркової недостатності з іншими захворюваннями, що могли викликати такі клінічні симптоми, як гіпоглікемічні стани, різке схуднення, гіпотензію, виражену м'язову слабкість, гіпонатріємію, гіперкаліємію. Обговорено основні принципи діагностики первинної надниркової недостатності, лікування та прогноз. Попри типові, специфічні прояви надниркової недостатності, діагностика в реальній клінічній практиці утруднена. Необхідна обізнаність та настороженість лікарів щодо симптоматики надниркової недостатності. Несвоєчасне виявлення хронічної надниркової недостатності може призводити до виникнення ускладнень. Своєчасні діагностика й лікування хронічної надниркової недостатності покращують прогноз захворювання та якість життя.

Ключові слова: надниркова недостатність; інсулінома; гіпоглікемія; гіпонатріємія; гіпохлоремія; гіпотензія; автоімунна тромбоцитопенія; хромогранін А