Diabetes mellitus and hyperhomocysteinemia

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Abstract. The article presents a clinical case of diabetes in patients with hyperhomocystein-emia. Late diagnosis of hyperhomocysteinemia in this patient led to difficulty in the choice of the tactics of hypoglycemic therapy. Secondary diabetes in a patient was found to be positive using insulin analogues and taking into account carbohydrate and folate diet. A combination of both pathologies (diabetes mellitus and hyperhomocysteinemia) requires monitoring of carbohydrate disorders and permanent therapy with vitamins B and folic acid.
Keywords: homocysteine, hyperhomocysteinemia, diabetes mellitus.

In 1932, scientists of the University of Illinois obtained a new amino acid (AMA) — homocysteine (HC) — a product of methionine demethylation [1]. In 1962, inborn errors of HC metabolism were first described in mentally retarded children, which manifested as homocysteinuria [2, 3]. In 1964, it was suggested that the possible cause of homotsysteinuria may be a birth defect of cystathionine-β-synthase enzyme that is clinically manifesting by vascular thromboembolic complications and lead to early death before the age of 30 years [4].

Homocysteine is a sulfur AMA with a free sulfhydryl group, which is an intermediate product of exchange of AMA methionine and cysteine. The only source of HC intake by the body is methionine contained in animal products. In the body, HC is formed by demethylation of methionine. Normally, its concentration in plasma is within the range 5 to 15 mmol/L [5]. Hyperhomocysteinemia (HHC) is diagnosed in case of increasing HC>15 mmol/L. A moderate degree of HHC is noted at a level of HC15-30 mmol/L, 30-100 mmol/L — at a middle level, and >100 mmol/L at a high HC degree. With age, a marked increase in HC is noted compared with children and adolescents. In men, HC levels are higher than in women by 2 mmol/L on average.

Various genetic defects of enzymes that participate in HC metabolism can lead to congenital HHC: cystathionin-β-synthase, methioninsynthases, methylenetetrahydrofolate reductases. The most common genetic cause of severe HHC is a homozygous deficiency of cystathionin-β-synthase. Clinically, it is manifested by a set of syndromes, lens abnormalities, osteoporosis, mental retardation, early atherosclerosis, skeletal deformities. Heterozygous mutation of this enzyme leads to a more moderate HHC.

Of particular importance in HHC development is a deficiency of vitamins B_6, B_{12}, folic acid, which reduces the activity of enzymes that are involved in HC metabolism. A deficiency of vitamins may be caused by their insufficient intake with food, gastro-intestinal diseases with mal-absorption.

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Increased plasma HC levels are noted in diabetes mellitus, due to the loss by the body of vitamins B [6]. A relationship was found between HHC and thrombosis — both arterial and venous [7] form. HHC leads to cerebrovascular disorders.

There is an interesting clinical case of diabetes mellitus in patients with hyperhomocysteinemia, which is mentioned below.

We have followed at the Therapy Department of Vinnitsa Regional Specialized Clinical Endocrinology Centre (VRSCEC) a patient A., aged 20 years. The patient was hospitalized with complaints of weight gain of 24 kg for 1.5 years, high fasting blood glucose, frequent hypoglycemia at night and during the day, fasting ketosis, headaches after hypoglycemic conditions.

Medical history: diabetes mellitus since 2012, diagnosed at 16 years old. Hospitalized in VRSCEC in 2012 with complaints of thirst, polyuria, weight loss of 8 kg, with acetone in the urine 4+ and blood glucose 19.0 mmol/L. Glyohemoglobin — 13.5%, C-peptide — 2.33 ng/ml (normal range 0,5-3,2 ng/ml). Height — 184 cm. Weight — 69 kg. BMI=20.3. The patient is known to be followed by a psychiatrist for the disease F 71.08 (middle degree of mental retardation). He is known having had a genetic examination in 2003 — no pathology found. Ophthalmologist's conclusion (2012) — subatrophy of optic nerve disks in both eyes. In 2012, diagnosis of type 1 diabetes, newly detected, glycemic control with high risk. Diabetic ketosis. Subatrophy of optic nerve disks of both eyes. Prescription at discharge: insulin Humulin R, H at a daily dose of 27 IU/day.

In 2013, hospitalization of the patient in VRSCEC due to complaints of frequent hypoglycemias. He reduced independently insulin dose to 20 IU/day. Dynamics of glyohemoglobin: 5.9%, 6.0%. The patient follows a diet. Self-monitoring of blood glucose 3-5 times a day. Diagnosis of 2013: Secondary diabetes mellitus (associated with an unspecified disorder), moderate, suboptimal glycemic control.

F 71.08. Subatrophy of optic nerve disks in both eyes. Recommendations: insulin therapy canceled, replaced by metformin at 2.000 mg / 24 h.

In 2014, hospitalization due to complaints of a weight loss of 19 kg per year, thirst, polyuria. The patient was over 14 months on metformin without insulin therapy. Blood glucose at admission: 17.0 mmol/L, urine acetone negative. At a general clinical and biochemical examination no changes were found. Basal C-peptide: 0.83 ng/ml (normal range 1.1-4.4 ng/ml); stimulated C-peptide: 1.8 ng/ml. Glyohemoglobin: 8.5%. Homocysteine — 32 mcmol/L (normal range 5.46-16.2 mcmol/L). Conclusion of MRI of brain: pineal gland cyst, internal aresorptive hydrocephalus, syndrome of liquor hypertension, arachnoidal cyst. The patient was examined by a genetician with the following diagnosis: gene polymorphism folate cycle-MTPP-2756 in homozygous condition. Neurologist's consultation: diabetic distal sensory polyneuropathy of feet, initial stage. Diagnosis of 2014 — secondary diabetes associated with genetic disorders. F 72.1. Disorder of sulfur amino acids' metabolism. Hyperhomocysteinemia. Subatrophy of optic nerve disks in both eyes. Recommended: folate diet, restriction of animal product proteins, group B vitamins' therapy. Patient on insulin Humulin R, H at a daily dose of 27 IU / 24 h.

Glycated hemoglobin in 2015 — 9.11%.

The examination during this hospitalization showed: height: 194 cm, weight: 85 kg, BMI=24.0. There were no data on obesity, despite an increase in weight of 24 kg. Evenly distribution of body fat, correct body type. There were no other objective abnormalities. Glycemic profile: 4-00-7.4 mmol/L; 8-00-12.3 mmol/L; 11-00-19.3 mmol/L; 14-00 -10.6 mmol/L; 17-00-13.1 mmol/L; 20-00-13.9 mmol/L. General clinical and biochemical tests have been performed. Complete blood count: Hemoglobin — 146 g/L; Er — 4.8×10^{12}/L; white blood cells — 4.7×10^{9}/L; erythrocyte sedimentation rate: 6 mm/h. Urinalysis: c/f, full transparency, specific weight: 1019; acidic reaction, no protein detected; leucocytes — 2-3 in sight. Urinary acetone at admission 4+. Daily proteinuria: no protein found. Urinary creatinine-albumin factor: 20 mg/g (normal range up to 30 mg/g). Creatinine — 89.0 mcmol/L (normal range 74-110 mcmol/L). Cholesterol — 6.0 mmol/L (normal range up to 5.2 mmol/L). Alat: 18 IU/L (normal range up to 50 IU/L). Fibrinogen — 3.4 g/L (normal range 2-4 g/L). Ethanol: negative test. Potassium: 4.3 mmol/L (normal range 3.5-5.3 mmol/L). Sodium: 139.6 mmol/L (normal range 135-148 mg/L); pH — 7.39. Glyohemoglobin: 8.6%. Homocystein — 9.34 mcmol/L (normal range 5.46-16.2 mcmol/L). ECG, ultrasound of

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the abdomen and thyroid have been performed. According to the results of examinations, no changes were detected. Ophthalmologist's conclusion: visus OD=0.6, OS=0.7; subatrophy of optic nerve disks of both eyes.

Tests showed high fasting blood glucose; two IU of insulin Humulin R were additionally administered to this patient at 6-00, in the presence of which fasting hypoglycemia was observed. In the morning, ketosis was often noted. During hospital treatment, the patient showed quite often nocturnal hypoglycemias (blood glucose at 4-00-2.6 mmol/L, 3.5 mmol/L) at a dose of 5 IU of Humulin N administered at 22-00. Due to diabetes lability, frequent ketosis and hypoglycemias, during this hospitalization the patient was transferred to insulins Epaydra, Lantus with a daily dose of 50 IU / 24 h. Glycemic profile at discharge: 4-00-7.0 mmol/L; 8-00-5.3 mmol/L; 11-00-7.3 mmol/L; 14-00-7.9 mmol/L; 17-00-7.0 mmol/L, 20-00-7.8 mmol/L. No ketosis and hypoglycemias were noted with insulin analogs. Diagnosis: Secondary diabetes mellitus (associated with genetic disorders F 72.1) of moderate degree, decompensation stage. Diabetic ketosis. Diabetic distal sensory polyneuropathy of feet, initial stage. Disorders of sulfur amino acids' metabolism. Hyperhomocysteinemia. Dyslipidemia. Subatrophy of optic nerve disks of both eyes.

Glyohemohlobin after 3 months: 7.2%, after 6 months: 6.2%. The patient is currently followed by an endocrinologist and psychiatrist. Besides insulin therapy, vitamins B_6, B9, B_{12}, folic acid are recommended to this patient.

In these patient group with hyperhomocysteinemia and disorders of carbohydrate metabolism (diabetes mellitus), it is of paramount importance to have full compensation of diabetes, stable therapy with vitamin B group and folic acid for a hyperhomocysteinemia, since these two diseases lead to atherosclerosis, diabetic complications (micro- and macroangiopathy), accelerate the development of osteoporosis. Metformin-containing medications are contraindicated in case of hyperhomocysteinemia.

Conclusions

1. Late diagnosis of hyperhomocysteinemia in this patient led to a difficulty in the choice of tactics of hypoglycemic therapy.
2. Secondary treatment of diabetes mellitus in patients with hyperhomocysteinemia was positive with insulin analogues and depends on the degree of carbohydrate metabolism disorder.
3. A combination of the two diseases (diabetes mellitus and hyperhomocysteinemia) requires a monitoring of carbohydrate disorders and permanent therapy with vitamins B group, folic acid.
4. Patients with combined pathology need a differentiated nutrition in the presence of carbohydrate metabolism disorders, based on folate diet.

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Сахарный диабет и гипергомоцистеинемия

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Резюме. В статье приведен клинический случай сахарного диабета у пациента с гипергомоцистеинемией. Поздняя диагностика гипергомоцистеинемии у данного пациента привела к затруднению в выборе тактики сахароснижающей терапии. Лечение вторичного сахарного диабета у пациента было положительным аналогами инсулина с учетом углеводной и фолатной диеты. Сочетание двух патологий (сахарного диабета и гипергомоцистеинемии) требует контроля углеводных нарушений и постоянной терапии витаминами группы В и фолиевой кислоты.

Ключевые слова: гомоцистеин, гипергомоцистеинемия, сахарный диабет.

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