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ECG DIGITALIZATION AND RARE DISEASES - FABRY DISEASE - OWN CLINICAL EXPERIENCE

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Fabry disease is a rare, *multi-system,* X-linked lysosomal storage *disorder* caused by mutations in the GLA gene, which encodes the enzyme α-galactosidase A [1,2]. Due to enzyme dysregulation there is an intracellular accumulation of glycosphingolipids, mainly globotriaosylceramide (Gb3) in various organs and tissues[3].

Symptoms are typically first experienced at the age of 10 years and manifests in the form of crises, the main signs of which are burning pain in hands and feet, paresthesia, hypohidrosis, fever. Full-scale clinical picture is observed in 2-3 years after manifestation of disease (skin – angiokeratomas; kidneys – the presence of protein in the urine, chronic kidney disease and kidney failure; cardiovascular system (CVS) – angina pectoris, left ventricular hypertrophy (LVH); eyes - dystrophic changes of the cornea; nervous system - chronic cerebrovascular failure) [4].

Pathological changes of CVS in patients diagnosed with Fabry disease occur due to direct effects on the heart and blood vessels of accumulated Gb3 with the development of LVH and fibrosis, as well as due to secondary hypertension, which occurs in the presence of renal pathology [5]. The accumulation of Gb3 in the cells of the conduction system, endothelial cells, valve fibroblasts and vascular smooth myocytes cause LVH, right ventricular hypertrophy, changes of conduction, valve dysfunction and microvascular angina[6].

The leading causes of reduced life expectancy of patients with Fabry disease - renal failure, cardiomyopathy, central nervous system dysfunction - can be corrected by the use of enzyme replacement therapy in combination with supportive care[7].

Clinical case. Patient A. was referred to hospital and complained of chest pain, burning pain in hands and feet, abdominal spots, headache and general weakness. He was hospitalized in the intensive care unit (ICU).

History of the present illness: the first clinical evidence appeared at the age of 7-8 years in the form of rash on the lateral surface of the abdomen and groin, then there were unpleasant sensations in the distal part of extremities (pain, numbness), fever, hight blood pressure (BP) (140-150 / 90-100 mm Hg). At the age of 16 - increase of neurological symptoms. Acute cerebrovascular accident was diagnosed (36 years - disease recurrence). At the age of 18 - a comprehensive study revealed proteinuria, at the age of 35 - the patient notes hearing problems. At the age of 40 he was diagnosed with cysts of both kidneys, hydrocalycosis of both kidneys, chronic pyelonephritis in remission. At the age of 42 - chronic kidney disease.

According to the results of preliminary examination:

Ultrasonic cardiography (UC) (left ventricle ejection fraction (LVEF) – 52 %. Concentric LVH with normal LV filling pressure (ventricular septum – 13 mm., wall of LV – 12 mm). Myocardial function of LV is satisfactory).

Electrocardiography (ECG) (LVH, shortening the time of atrioventricular conduction).

Holter monitoring of ECG (atrial extrasystolic arrhythmia).

Consultation by a cardiologist: Hypertensive disease II stage, cardiovascular risk 4. Atrial extrasystolic arrhythmia. Heart failure II A with preserved ejection fraction of LV (52%), functional class II.

Magnetic resonance imaging of the brain (MRIB) (the detected changes may correspond to the lesion of the corticospinal tract, cyst of the pineal gland).

Computed tomography of the thoracic cavity (emphysematous lung changes, pneumofibrosis).

DNA-diagnostics (in the GLA gene - hemizygous variant of g. (Gly 138Arg) exon 3. The mutation belongs to the pathogenic, first class).

Enzyme diagnostics (alpha-galactosidase activity <2.5 nmol/h/mg, normal rate> = 15.3 nmol/h/mg) is below normal).

Lyso-Gb3 in blood: 55,3 ng/ml (normal rate <= 1,8 ng/ml) is above normal.

According to the clinical anamnesis and results of additional examination, the patient was diagnosed with an inherited metabolic disorder from the group of diseases of lysosomal accumulation - Fabry disease, X-linked manner.

Data of examination of the patient by the doctor (ICU): general state of the patient – moderately severe; consciousness – preserved; position – active; skin – dry, rash on the back and sides of the abdomen; lymph nodes - not palpable; heart sounds - weakened, rhythmic; lungs - vesicular breathing, weakened in the lower parts; Pasternatsky's symptom is negative on both sides, no swelling. Heart rate (HR) - 62/ min, respiratory rate - 18/min, BP - 155/90 mm Hg, body temperature - 36.6 °C.

Standard ECG was performed at admission. It was noted that in II, III standard leads and in aVF oblique ascending depression of ST segment up to 1.5 mm in III and

aVF, and up to 0.5 mm in II standard lead is registered. The oblique ascending elevation of the ST segment was also registered in the chest leads V1-V4 with an increase from 0.5 mm in V1, 0.7 mm in V2, to 1.3-1.5 mm in V3 and V4, respectively, that required differential diagnosis with acute coronary syndrome (ACS). Signs of LVH and shortening of the PQ interval were noted (Fig. 1).

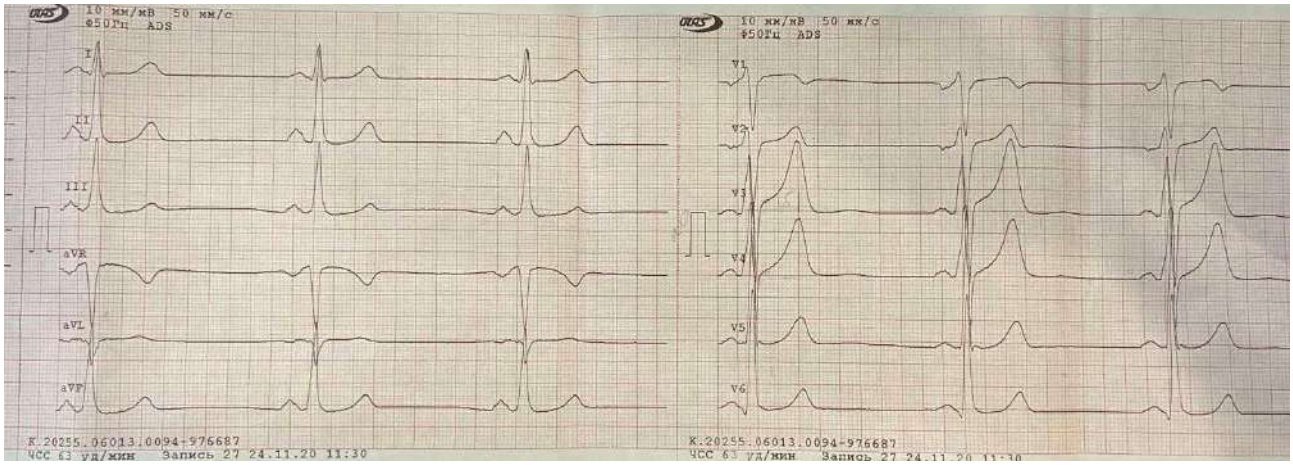

Fig.1 ECG of a patient with a diagnosis of Fabry disease

Subsequently, an analysis of the «digitized» ECG was performed to determine the parameter of the differentiated wave T - the ratio of maximum speeds (MSR) [8] and parameters «ST slope» - the angle β of the slope of the segment ST (βº) and the height of its extension H (H, mm) [9]. It was found that the MSR did not confirm the ischemic nature of the changes in the T wave and was more characteristic of LVH: in leads II, III, aVF it was equal to 5.16; 3.66 and 2.87, respectively, and in the chest leads V2-V4 - 5.7; 7.26 and 5.37, respectively. Similarly, the analysis of changes in the indicators of «ST slope» showed that the nature of depression of the STsegment in leads II, III and aVF was «benign» oblique ascending type: the angle βº in II, III, aVF was equal to 8,64º; 9.71º and 9.87º, respectively [10]. Regarding the height of elongation of the angle βº H, it also did not have critical indicators: H in II, III, aVF was equal to 0.76; 0.86 and 0.87 mm, respectively. Similarly, changes in the ST segment in leads V2-V4 also did not indicate acute myocardial ischemia, and were «benign» oblique type [11]. The angle βº in V2, V3, V4 was equal to 13.24º; 25.7º and 37.69º, respectively. As for the height of its extension H, it was 1.18; 2.41 and 3.86 mm, respectively.

Because the patient had been previously diagnosed with Fabry disease, he was given an alpha-agalsidase infusion («*Raplagal*») 7,0 ml + 0,9 % sodium chloride solution 100,0 IV. The patient was previously given 1.0 suprastin and 8 mg of dexamethasone. The recommended intake of the following drugs: acetylsalicylic acid 100 mg (continuously), ramipril 2.5 mg (continuously), carbamazepine 200 mg in 2-4 doses. After administration of the drug, the patient showed improvement in health, stabilization of BP (120/75 mm Hg). The changes on the ECG after treatment were interesting (Fig. 2).

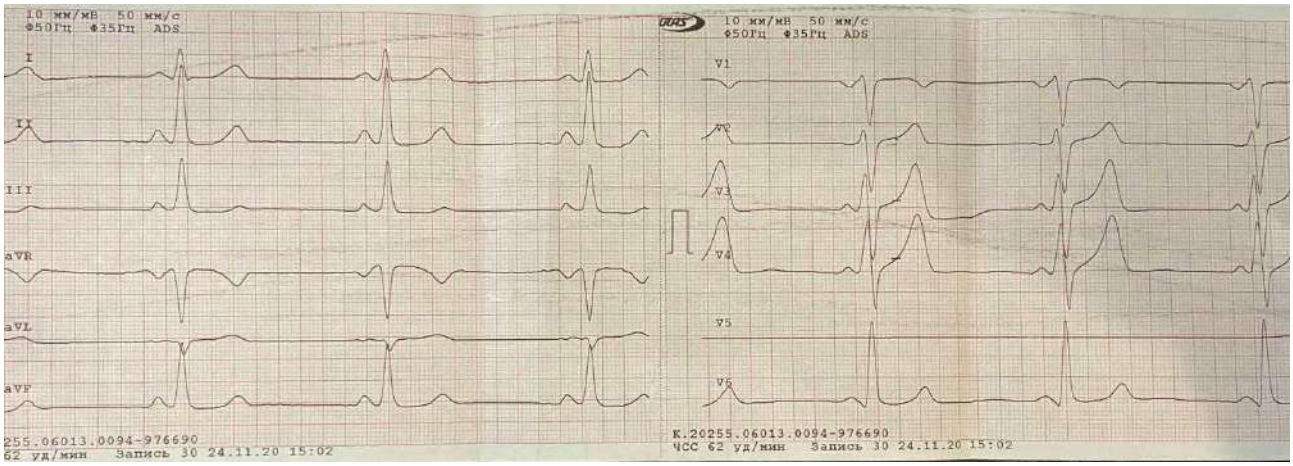

Fig. 2 ECG of the patient A. after treatment

The main changes concerned a decrease in the magnitude of ST segment depression in II, III and aVF and ST segment elevation in V2-V4. The values of the angle βº and the height of its elongation H (mm) decreased on average for leads II, III, aVF by 43.2 ± 1.1%, and for leads V2-V4 by 25.1 ± 1.2%. Similar changes concerned the MSR indicator: in leads II, III and aVF its value decreased to 2.1; 1.77 and 1.8, respectively. Regarding thoracic leads, the values of MSR - V2-V4 also decreased to 2.69; 2.13 and 2.38, respectively, and practically approached the reference values for LVH [8].

Fabry disease belongs to orphan diseases and due to the expansion of the arsenal of diagnostic methods recently found a much larger number of cases of this pathology [5]. Agalsidase alfa and agalsidase beta are used for the pathogenetic treatment of Fabry disease, and experience of recent years has shown a reduction of the progression of LVH, better prognosis and a reduction of the amount of cardiovascular events. [5]. The effectiveness of treatment is better in younger patients and with less severe renal impairment in the initial stages of therapy [5]. It is also worth noting that early treatment helps to prevent the accumulation of lipids, the continuous progression of the disease and irreversible damage to various organs [12].

Treatment of cardiovascular complications of patients with Fabry disease is symptomatic (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are used to treat hypertension and provide renoprotection; anginal attack – antiplatelets; bradyarrhythmias - implantation of an artificial pacemaker; dangerous ventricular tachyarrhythmias - installation of a cardioverter defibrillator) [5].

The diagnosis and treatment of patients with Fabry disease should involve a multidisciplinary team of specialists - neurologists, cardiologists, dermatologists, ophthalmologists and others. [5]. When Fabry disease is detected, it is also necessary to conduct examination of the patient's relatives - especially relevant for young people, as timely enzyme replacement therapy can improve the duration, prognosis and quality of life. [5].

This clinical case demonstrates that the clinical manifestation of Fabry disease is associated with damage to various body systems, which were detected according to the examination results - ECG, UC, MRTB, DNA diagnostics, enzyme diagnostics, etc. Thus, due to the use of digital ECG processing, certain characteristic features of the ECG were established in a patient with a confirmed diagnosis of Fabry disease,

differential diagnosis with ACS was performed and the «non-ischemic» nature of these changes was proved, which corresponds to the general idea of this disease.

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