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GALACTOSEMIA TYPE I: A CASE FROM PRACTICE

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Abstract. Galactosemia is a hereditary disorder of carbohydrate metabolism, as a result of mutation of genes encoding enzymes involved in galactose metabolism. With late diagnosis and the absence of pathogenetically justified diet therapy, the disease can lead to multiple organ failure and death. The article presents the issues of pathogenesis, clinical manifestations, diagnosis and principles of dietary therapy of galactosemia in children. The author presents his own clinical observation, which highlights a complex example of differential diagnosis of galactosemia with intrauterine infection in a child in the neonatal period.

Key words: *galactosemia; clinical case; screening.*

ГАЛАКТОЗЕМИЯ I ТИПА: СЛУЧАЙ ИЗ ПРАКТИКИ

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Резюме. Галактоземия — наследственное нарушение обмена углеводов, возникающее в результате мутации генов, кодирующих ферменты, которые участвуют в обмене галактозы. При поздней диагностике и отсутствии патогенетически обоснованной диетотерапии заболевание может привести к полиорганной недостаточности и летальному исходу. В статье изложены вопросы патогенеза, клинических проявлений, диагностики и принципов диетотерапии галактоземии у детей. Представлено собственное клиническое наблюдение, где освещен сложный пример дифференциальной диагностики галактоземии с внутриутробной инфекцией у ребенка в неонатальном периоде.

Ключевые слова: *галактоземия; клинический случай; скрининг.*

INTRODUCTION

Timely diagnosis of congenital metabolic disorders in a newborn child remains a topical issue of pediatrics [1].

Galactosaemia is a hereditary disorder of carbohydrate metabolism that occurs as a result of mutation of genes encoding enzymes that are involved in galactose metabolism. As a result of these disorders, an excess of galactose and its metabolites (galactose-1-phosphate and galactitol) accumulates in the body, which determines the clinical picture of the disease and the formation of delayed complications.

The type of inheritance of galactosaemia is autosomal recessive. The incidence of the disease in the Russian Federation is 1:20 000, with the vast majority of cases of the disease caused by mutations in the GALT gene (classical galactosaemia type I).

The main carbohydrate component of breast milk and infant formula is lactose, a disaccharide

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consisting of two monosaccharides, galactose and glucose. Despite the great similarity between the molecules of glucose and galactose, the conversion of the latter into glucose requires several enzymatic reactions [2].

Galactosaemia combines several genetically heterogeneous forms. The disease is based on the deficiency of one of the three enzymes involved in galactose metabolism: galactose-1-phosphate uridyltransferase (GALT), galactokinase (GALK) or uridine diphosphate (UDP)-galactose-4-epimerase (GALE). The abnormality of one of these enzymes is genetically caused by mutations in the genes encoding the protein structure of the enzyme molecule, leading to the synthesis of a defective enzyme and a significant decrease in its activity. As a result, the normal metabolism of galactose is blocked and a large number of toxic substances are formed (galactonate, galactitol, galactose-1-phosphate, etc.), which, along with galactose, accumulate in the blood and provoke the development of severe lesions of internal organs (liver, brain, kidneys), manifested by polymorphism of implictations [3–5].

Galactose is essential for the growth and development of the child's body. This monosaccharide is not only a source of energy for the cell, but also plays an important role as prebiotic, serving as a necessary plastic material for the formation of glycoproteins, glycolipids and other complex compounds used by the body to form cell membranes, nerve tissue, nerve endings, myelination of neurons, etc. The main source of galactose in humans is food. The large amount of food consumed during the day (primarily dairy) contains lactose, from which galactose is formed in the intestines as a result of hydrolysis [6].

There are three types of galactosaemia depending on the patient's defect of one of the three major enzymes involved in galactose metabolism:

- classical — galactosaemia type I, caused by deficiency of the GALT enzyme, includes the Duarte variant galactosaemia (decreased enzyme activity);
- galactosaemia type II — GALK deficiency;
- galactosaemia type III — GALE deficiency.

Classic galactosaemia manifests itself in the neonatal period during feeding with breast milk or infant formula. Manifestations of the disease may include abundant regurgitation, vomiting, diarrhea, lack of weight gain, lethargy, drowsiness, and later — signs of malnutrition, stunting and retardation of psychomotor development. In the absence of timely diagnosis and pathogenetically justified diet therapy, symptoms of liver disease appear and increase, accompanied by hypoglycemia, jaundice, hepatosplenomegaly, and hemorrhagic syndrome. In the neonatal period, patients with galactosaemia, due to the suppression of protective immune reactions, have an increased risk of developing sepsis caused by Escherichia coli (E. coli), which often leads to death. The disease progresses rapidly and in the absence of treatment is life-threatening.

Neonatal screening is recommended for all newborns to identify inherited disorders of galactose metabolism. Diagnostics is aimed at determining the concentration of total galactose in a dried blood spot; if the result is positive, the activity of the GALT enzyme and major mutations in the GALT gene are determined [4].

The main method of treating galactosaemia is diet therapy, which involves lifelong exclusion from the diet of products containing galactose and lactose. The patient should completely refrain from eating any kind of milk (female, cow, goat, infant formula, etc.) and all dairy products, as well as carefully avoid those products in which they can be added: bread, pastries, caramel, sweets, margarine, etc. The use of low lactose milk and infant formula is also prohibited. It should be taken into account that a number of products of plant origin contain oligosaccharides — galactosides (legumes (peas, beans, lentils, mung beans, chickpeas), soybeans (but not soy protein isolate), spinach, cocoa, chocolate, nuts), and in products of animal origin — glycoproteins (liver, kidneys, brains and other by-products), which under certain conditions can be split and be a source of galactose [3].

In the formulation of therapeutic diets for children in the first year of life with the disease, the amount of basic food ingredients and energy should be in accordance with age-specific physiological standards. Breast milk and/or infant formula should be replaced with lactose-free formulas adapted to their composition. To treat patients with galactosaemia, specialized infant formulas based on soy protein isolate (Bellakt Soya, Nutrilak Soya, Nutrilon Soya, Frisosoy) or extensively hydrolyzed whey are used — in case of allergy to soy protein. Formulas based on synthetic amino acids and lactose-free, casein-dominant infant formulas are also used. It is not recommended to use lactose-free whey protein-dominant baby formulas with a predominance of whey proteins (60% or more). These infant formulas may contain trace

amounts of galactose. Specialized infant formulas are introduced into the diet of patients with galactosaemia within one day, immediately after diagnosis. Patients are strictly recommended to introduce lactose-free complementary foods and a lifelong lactose-free diet.

It is not recommended for patients of any age to use medications containing lactose/galactose, as well as homeopathic remedies, tinctures and alcoholic drug forms. Thus, lactose is often used as an excipient in homeopathic medicines, and ethanol inhibits the elimination of galactose from the liver [3].

The outcome and course of the disease are influenced by the timing of diagnosis, timely and adequately prescribed diet treatment and emergency measures (transfusion of blood substitutes, infusion therapy). The prognosis of the disease is unfavorable in late-diagnosed severe forms of galactosemia (due to the lack of screening). With timely treatment, the prognosis for the life and development of patients is significantly improved.

AIM OF THE STUDY

The aim is to examine the clinical manifestations and differential diagnosis of the disease using the example of a particular patient with galactosaemia.

CLINICAL CASE

We present a case of observation of a patient with classical galactosaemia type I based on examination of a child, study of his medical history and outpatient card.

A 10-day-old girl with complaints of severe jaundice of the skin was admitted to the neonatal pathology department of the Republican Children's Clinical Hospital in Donetsk.

The child was born in the maternity hospital of Torez, Donetsk People's Republic. A child from the fourth pregnancy, flowing on the background of colpitis, polyhydramnios, and gestational hypertension. The mother suffers from nicotine dependence and continued to smoke during pregnancy. At 11 weeks, she was examined at the medical genetic center — no pathology was found. Fetal ultrasound was performed 3 times — no pathology was detected. Previous pregnancies: first pregnancy — normal delivery, second — miscarriage at 10 weeks, third — normal delivery. This delivery is the fourth, premature, at 36 weeks of dichorionic diamniotic twins, by cesarean section due to the transverse baby position. The child was born as the second of twins with a weight of 2300 g, length — 47 cm. Apgar score was 7–8 points. The child Screamed immediately. She was bottle-fed with expressed mother's breast milk. On the 2nd day of life, skin and scleral icterus appeared: total bilirubin — 205 μmol/l due to the indirect bilirubin. On the 9th day of life, total bilirubin was 388 μmol/l, direct bilirubin was 67.6 μmol/l.

For the first 9 days of life in the maternity hospital, the child received phototherapy, ursodeoxycholic acid preparations, bifidumbacterin, and vitamin D3 aqueous solution. There were no positive changes in the child's condition. On the 10th day of life, the child was transferred to the neonatal pathology department of the Republican Children's Clinical Hospital in Donetsk.

The general condition of the child on admission to the clinic is serious. There are symptoms of prematurity and immaturity. Newborn and spinal cord reflexes are depressed, and oral reflexes are evoked. Muscle tone is dystonic, spontaneous motor activity is reduced. Anterior fontanelle 3.0×4.0 cm, at the level of the skull bones. Natural feeding — expressed breast milk. Visible mucous membranes and skin are icteric and clean. Tissue turgor and skin elasticity are reduced. The subcutaneous fat layer is thinned. Peripheral lymph nodes are not enlarged. Above the lungs, on percussion is a normal pulmonary sound, auscultation is puerile respiration, wheezing is not heard. The boundaries of relative cardiac dullness are within the age norm. Heart sounds are muffled, rhythmic, systolic murmur over the entire area of the heart. The abdomen is palpable, symmetrical, increased in volume. Peristalsis is active. The liver is palpated at 4.0 cm below the costal margin. The kidneys and spleen are not palpable. The stool is mushy, yellow, mixed with mucus. Urine is dark yellow.

The child was examined in the department.

Complete blood count revealed mild anemia, which persisted over time, and an increased erythrocyte sedimentation rate (ESR).

Biochemical blood test on admission showed hyperbilirubinemia (total bilirubin up to 440 μmol/l, direct bilirubin — 175 μmol/l), elevated transaminase levels (aspartate aminotransferase (AST) — 109 U/l, alanine aminotransferase (ALT) — 67 U/l).

Coprocytogram: neutral fat + +, leukocytes — 8–10 in the field of view.

Stool, nasopharyngeal and umbilical wound culture — pathogens and opportunistic pathogens not detected.

Kidney ultrasound is normal.

Abdominal ultrasound: in the abdominal cavity between the liver and diaphragm, along the round ligament of the liver, as well as between the spleen, stomach and intestines, along the flanks, in the lesser pelvis free fluid with fibrin threads and finely dispersed suspension is determined. The peristalsis in small intestine is sluggish. The wall of the small intestine on the visualized fragment is thickened to 1.5 mm, there is liquid content in the lumen of the large intestine.

Neurosonography: echo signs of brain immaturity, hypoxic-ischemic brain injury; hemodynamics are not changed.

Consultation of neurologist: mild hypoxic ischemic encephalopathy of the 1st degree. Cortical excitation.

Consultation of ophthalmologist: consultation: bilateral cataract.

Based on the clinical picture and additional examination data, the child was suspected of having an intrauterine infection, hepatitis, enterocolitis against the background of prematurity and immaturity.

Received treatment: feeding with the Belakt, then Nutrilon, antibiotic therapy (cefipime, amikacin), 10% glucose solution, 0.9% NaCl solution, aminoven solution, calcium gluconate, ursodeoxycholic acid preparations, bifidumbacterin.

During screening at the medical genetic center, an increase in galactose to 90 mg/dc was noted; during the repeat study on the 16th day, the galactose level remained elevated to 66.33 mg/dc. The child was consulted by a geneticist and galactosaemia was diagnosed. Prescribed diet with the exclusion of galactose, lactose, and a transition to feeding an infant formula based on soy protein isolate.

It is recommended to dynamically examine the level of galactose, blood biochemistry test, and abdominal ultrasound.

During the telemedicine conference, the child was consulted at the National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov. Based on the presented data, a late preterm infant has a clinical picture of galactosaemia.

Based on genetic molecular testing, the child has two mutations of the GALT gene — type I galactosaemia was diagnosed.

Biochemical blood test: triglycerides — 0.87 mmol/l, cholesterol — 3.69 mmol/l, alkaline phosphatase — 461 U/l, albumin — 34.0 g/l, calcidiol — 6.1 ng/ml, urea — 4.4 mmol/l, glucose — 2.9 mmol/l, protein — 60 g/l, creatinine — 27 μmol/l, calcium — 2.31 mmol/l, potassium — 4.3 mmol/l, sodium — 142 mmol/l.

Coagulogram: fibrinogen — 2.08 g/l, prothrombin time — 16.3 s, activated partial thromboplastin time (aPTT) — 30.4 s, thrombin time — 14.9 s, international normalized ratio (INR) — 1.35.

During observation, against the background of pathogenetically justified diet therapy and drug treatment, the child's condition improved. There was a positive dynamics of body weight gain, the peritoneal effusion and the icteric staining of the skin and sclera gradually disappeared. As a result of the treatment, motor activity was fully restored, the reaction to the examination was adequate, muscle tone in the extremities was normalized. There is puerile breathing in the lungs, the heart sounds are muffled, rhythmic, the abdomen is soft and painless on palpation, the liver is + 2.5 cm below the costal margin. The stool is mushy, yellow, the urine is light.

On abdominal ultrasound and Doppler ultrasound of the portal system in dynamics after a month of therapy: the parenchymal organs of the abdominal cavity are not changed; there are no signs of portal hypertension or hepatic vein obstruction.

In satisfactory condition, the child was discharged for follow-up with a local pediatrician, neurologist, and geneticist. Parents were given recommendations on diet therapy, the introduction of complementary foods, vitamin D3 aqueous solution 4000 IU/day was prescribed for a course of 1 month with a transition to a prophylactic dose of 1000 IU/day for a long time, ursodeoxycholic acid preparations of 15 mg/kg per day were recommended.

CONCLUSION

Galactosaemia is a serious hereditary disease caused by metabolic disorders of galactose and, as a result, lactose intolerance. The disease manifests itself in the first days of life and can be extremely difficult with the rapid development of multiple organ disorders. With the earliest possible diagnosis, timely initiation of pathogenetically justified diet therapy and its strict adherence, the prognosis for the life and development of a child with classical galactosaemia is quite favorable. The presented clinical example points out the difficulties of differential diagnosis of galactosaemia

with intrauterine infection. Screening allowed us to diagnose galactosaemia in the child.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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