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Case Report

Galactosemia Type I in a Child with Heterozygous Mutations (Own Observation): A Clinical Case

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ABSTRACT

Galactosemia is a rare metabolic disease, and late diagnosis can lead to severe liver injury. We present a clinical case of galactosemia type I that manifested during the late neonatal period with vomiting, cholestatic liver injury, coagulopathy with hemorrhagic syndrome, and poor weight gain. Differential diagnoses included necrotizing enterocolitis and intestinal obstruction. The residual activity of the GALT enzyme corresponded to the biochemical variant but did not match the severity of the clinical presentation. On a lactose-free formula, the child's condition improved. Genetic testing identified two pathogenic heterozygous mutations in exons 3 and 6 of the GALT gene. Subsequent observation revealed delayed motor development by the end of the first year of life.

Keywords: Galactosemia; Metabolism; Children; Screening; Mutation; Diet Therapy

Introduction

Galactosemia is a rare inherited metabolic disorder caused by enzyme deficiencies involved in galactose metabolism. Three main types are recognized: classic galactosemia (GALT deficiency), galactokinase deficiency (GALK), and UDP-galactose-4-epimerase deficiency (GALE). The Duarte variant is characterized by a biochemical decrease in GALT enzyme activity without clinical manifestations. Japanese authors have described type IV galactosemia, associated with mutations in the GALM gene encoding galactose mutarotase [1].

With a deficiency of any of the enzymes, galactose is not converted into glucose, toxic galactose metabolic products accumulate and affect the brain, liver, reproductive organs, and lens of the eye, leading, in the absence of a diet, to irreversible consequences and death [2].

The disease debuts a few hours-days after the start of milk-formula feeding with dyspepsia, hypoglycemia, rapidly progressive liver failure with cholestasis syndrome and coagulopathy [3]. The toxic effect of galactose metabolites on neutrophils contributes to a high incidence of sepsis in newborns, which, along with severe acute liver failure, is the main cause of death in neonatal patients [4, 5]. In the absence of a dairy-free diet, liver damage can progress rapidly with the development of cirrhosis with an unfavorable outcome. A fatal case of a 2.5-month-old infant with galactosemia, with biliary cirrhosis of the liver, due to parents' incompetence to carry out therapeutic nutrition has been described [6]. At the same time, there are separate reports of patients with the development of periportal and intra-lobular fibrosis in the first month of life and complete reversibility of morphological changes after the introduction of dietary nutrition [7]. Liver lesions can be combined with cataracts that occur at birth or in the neonatal period [8].

The frequency of galactosemia has an ethnic predisposition, occurring more often, for example, among infants in Ireland - 1:23500-1:44000, with the highest rates in the group of travelers (Irish nomads) - 1:430 [9]. The lowest incidence is observed among people of Swedish and Japanese descent, as well as in Taiwan [2, 10]. In the Russian Federation, the frequency of galactosemia type I is 1:20,000 [11]. The most common mutation is c.563A>G(p.Gln188Arg), which occurs in 70% of cases in patients of the European population, and the mutation p.Ser135Leu (c.404C>T) is more typical for African Americans [12, 13].

In the Ryazan region during the period from 2008-2021, 154706 newborns were examined, 4 cases of galactosemia type I were detected (in 2008, 2009, 2010 and 2020), the frequency was 1 per 38,676 live births. In 2022, a fifth case was identified, which we represent.

Clinical Case Presentation

Child N., from 2 pregnancies (the first child is healthy), at term, birth weight 3210 grams, height 51 cm, head circumference -34cm, chest circumference -34cm, on the Apgar scale 8/9 points. After neonatal screening, the child was discharged home for 4 days of life. Vaccinated against hepatitis B, tuberculosis. According to the screening results, the level of galactose in the blood was 75 mg/dL (with a norm of no more than 10 mg/dL). A repeat test at 21 days showed a level of 100 mg/dL. The boy was consulted by a geneticist at the medical and genetic center and sent for hospitalization, where he was admitted on the 23rd day of his life due to persistent jaundice.

Upon admission to the regional children's clinical hospital, the child's condition was assessed as severe due to symptoms of intoxication, severe anemia, jaundice, and poor weight gain. Weight 3105 grams (-105 grams of birth weight), length 52 cm (+1 cm). The temperature is 36.7 C. Upon examination, the child was sluggish, the reflexes of newborns were rapidly depleted. The skin is pale, with an icteric tinge. Tachypnea 50 per minute, heart rate 150 beats per minute, SpO2 97% without oxygen. There was no wheezing in his lungs. The abdomen is swollen, painless, bowel sounds were absent. The liver is +2,5 cm from the edge of the costal arch. There was no stool during the examination, the diuresis was not disturbed.

Blood tests on admission showed severe anemia, leukocytosis, hyperbilirubinemia, decreased total protein level, increased liver values, alkaline phosphatase. Due to the ongoing decrease in hemoglobin level (68 g/L), the child underwent blood transfusion. (Table 1)

Clinical and laboratory manifestations of liver failure were noted: hemorrhagic syndrome (bleeding from blood sampling sites), low fibrinogen levels, a decrease in the prothrombin index, prolonged activated partial thromboplastin time, D-dimers were negative. (Table 2). The child received fresh frozen plasma.

When examined herpes simplex virus types 1 and 2., cytomegalovirus, Epstein-Barr virus, toxoplasmosis was not detected. No radiological evidence of pneumonia was found. Echocardiography and brain ultrasound of the brain, an examination by an optometrist and a neurologist revealed no pathology.

In the first day after admission, the child had a clinic of small intestinal obstruction: bloating, anxiety. Abdominal X-ray showed irregularly distended

intestinal loops. During the observation, the diagnosis of intestinal obstruction was ruled out, the clinic was regarded as necrotic enterocolitis.

Along with antibacterial (ceftriaxone, amikacin), red blood cell transfusions, infusion therapy with elements of parenteral nutrition, the child was immediately transferred to soybean formula feeding. Against the background of treatment, positive clinical dynamics were noted: the boy became more active, absorbed the enteral load, and began to gain weight. Stabilization of laboratory parameters was noted: liver enzymes and bilirubin were normalized. Blood test showed grade 1 anemia and no leukocytosis. Fibrinogen, prothrombin index, activated partial thromboplastin time were normal. (Tables 1 and 2).

Table 1. Dynamics of laboratory scores of patient before and after treatment

Indicators	Hb, g/l	WBC, мм 3	GLU, mmol/l	Total protein, g/l	BIL-T/D-BIL, mmol/l	ALP	ALT/ AST
Initial values	74	25800	2,8	38,8	282/69	1081	83/173
After treatment	91	8700	5,7	49	25,6	240	20

Table 2. Patient coagulation before and after treatment

Indicators	Fibrinogen, g/ l	Activated Partial thromboplastin Time, sec	D-dimer
Initial values	1,77	43,3	negative
Progression	0	>120	negative
After treatment	2,0	33,7	negative

The child was discharged on day 50 of life in a stable condition, having gained +600 g since admission (+400 g since birth). He continued feeding with soy mixture, followed by an increase in volume, repeated genetic counseling and determination of enzyme activity and major mutations in the GALT gene.

At the age of 3 months, enzyme diagnostics was performed at the N.P. Bochkov Moscow State Medical University by spectrometry: The activity of the enzyme galactose-1-phosphaturidyltransferase was 2.14 E/rHb (reference values 4.4–15 E/rHb). At the age of 4.5 months, the boy was re-examined at the MGNC named after N. P. Bochkov. The GALT gene MIM 606999; RefSeq: NM 000151.3), galactosemia type I (OMIM 230400) was analyzed using direct automatic sequencing by Sanger. An autosomal recessive type of inheritance. A variant of the nucleotide sequence C. 267CG (p. Tyr89Term) in a heterozygous state was identified in exon 3. The variant is described in the HGMD mutation data base (CM1925804). A frequent mutation of C.563A (p.Gln188Arg) in a heterozygous state was found in exon 6. Based on the genetic test, type I galactosemia was verified.

Subsequently, the child was observed in the medical rehabilitation department at the place of residence. The galactose level was normal, and the child received lactose-free formulas and complementary foods. At the age of 7 months, the child's physical development was age appropriate. There was low muscle tone, he did not turn from back to stomach, did not raise the upper part of the body with support on his hands, lying on his stomach, did not sit up on his own. After repeated rehabilitation courses, by the age of 10 months, motor development improved somewhat: he began to sit up on his own. Currently, the child continues to be observed by a neurologist and undergoes rehabilitation courses.

Discussion

The presented case demonstrates a severe course of galactosemia with liver damage and hemorrhagic syndrome manifested in the late neonatal period. Elevated total galactose (100 mg/dL) was combined with a moderate decrease in GALT enzyme activity of 2.14 E/rHb (24% of normal), which corresponds to a low-symptomatic variant of the disease. However, the clinical picture was closer to classical galactosemia.

Attention is drawn to the discrepancy between moderately reduced enzyme activity, high galactose levels, and severe clinical presentation. It should be borne in mind that the GALT enzyme is detected in red blood cells, but its activity in different tissues, in particular in hepatocytes, may vary. The enzyme level is not always evidence of a favorable course, and therefore it is necessary to critically evaluate the clinical picture.

Our patients were analyzed for the GALT gene using direct automatic Sanger sequencing. In exon 6, a frequent mutation c.563A (p.Gln188Arg) was detected in the heterozygous state, which is most often detected in the Russian Federation, and in the homozygous state it is manifested by the most severe classical version of galactosemia [14, 15]. In exon 3, a variant of the nucleotide sequence c. 267C → G (p. Tyr89Term) in the heterozygous state. Examination of the patient's parents revealed a mutation c.563A (p.Gln188Arg) in the heterozygous state in the mother and c. 267C → G (p. Tyr89Term) - at the father.

Variant c. 267C → G (p. Tyr89Term) is a nonsense mutation: a single nucleotide replacement of cytosine with guanine leads to the appearance of a stop codon at position Tyr89 and stops further protein synthesis.

This variant with. 267C → G (p. Tyr89Term) was first identified in the ClinVar database in 2023 as SCV004198542.1. A recent entry in the 28.01.2026 National Library of Medicine identifies this variant as (SCV006562472.1) probably pathogenic. The frequency of this variant is characterized as extremely rare in the general population. One vehicle was identified during preconceptional screening. The information search did not reveal any mention of the detection of this variant in patients with galactosemia or their relatives in either the homozygous, heterozygous or compound-heterozygous variant.

Conclusion

Thus, the patient's compound heterozygous mutations c.563A>G (p.Gln188Arg) and c.267C>G (p.Tyr89Ter) correspond clinically to a variant of galactosemia close to the classic form, manifesting with severe liver damage in the late neonatal period.

The severity of galactosemia is determined by the heterogeneity of mutations, the degree of enzymatic deficiency, and the rate at which a child is transferred to a lactose-free diet. Genetic research expands our understanding of the variety of disease variants and allows us to trace clinical and genetic correlations.

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