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Neonatal diabetes mellitus – manifestation of GATA-6 syndrome

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ABSTRACT

GATA6 syndrome is an unusual genetic disorder that presents complications during pregnancy, congenital heart defects, neonatal diabetes, and severe pancreatic dysfunction. The cause of the syndrome is a de novo mutation in the GATA6 gene, located on chromosome 18. We present the case of a patient who exhibited congenital heart defects and severe hyperglycemia from the neonatal period, caused by pancreatic agenesis. The diagnosis was established based on molecular genetic analyses. Insulin and pancreatic enzyme replacement therapy provide a favorable prognosis in pancreatic agenesis, significantly reducing neonatal mortality associated with this drastic diagnosis.

Keywords: GATA6 syndrome, neonatal diabetes mellitus, pancreatic agenesis, children

INTRODUCTION

Neonatal diabetes mellitus (NDM) is a rare metabolic disorder characterized by persistent hyperglycemia within the first 6 months of life and low insulin levels [1]. The incidence of NDM varies between 1 in 90,000 to 1 in 160,000 live births, with variations across different ethnic groups. Diabetes mellitus (DM) diagnosed within the first 6 months is most likely to be of monogenic origin. Thus, among all cases of NDM, approximately 80% are of monogenic cause [2]. In countries where consanguineous marriages are common, more cases of NDM are encountered, most often in association with rare syndromes [3]. The pathogenesis of NDM is presented by the following mechanisms:

1. Deterioration of pancreatic β-cells – in INS, EIF2AK3, IER3IPI, FOXP3, WFS1 syndromes.
2. Hypoplasia or agenesis of the pancreas – in PDX1, PTF1A, HNF1B, MNX1, RFX6, GATA4, GATA6, GLIS3, NKX2-2, NEUROG3, NEUROD1, PAX6 syndromes [4].
3. Alteration of pancreatic β-cell function, affecting insulin synthesis or secretion – in KCNJ11, ABCC8, GCK, INS, RFX6, SLC2A2, SLC19A2 syndromes [5].

Genes implicated in the pathogenesis of NDM include: KCNJ11 (50%), FOXP3, ABCC8, INS, GATA6, EIF2AK3, GCK, PTF1A, GLIS3, PDX1, SLC19A2, GATA4, NEUROD1, NEUROG3, NKX2-2, IER3IP1, MNX1, 6q24, ZFP57, HNF1B, DPZ, DZT [6].

NDM presents in two clinical forms: transient neonatal diabetes mellitus (TNDM), which does not require long-term treatment and remits by 12 weeks of life; however, approximately 50% will develop type 1 diabetes during childhood or adolescence, and permanent neonatal diabetes mellitus (PNDM), which is rarer, has no remission periods and requires lifelong insulin replacement therapy [7].

GATA6 syndrome is an unusual genetic disorder that presents complications of pregnancy, congenital heart defects, and severe pancreatic dysfunction. The cause of the syndrome is a "de novo" mutation in the GATA6 gene, located on chromosome 18. The risk of having another child with this mutation in the family is less than 1%. Studies have shown that 50% of cases of pancreatic agenesis and at least 3% of neonatal diabetes mellitus (NDM) are caused by mutations in the GATA6 gene [8]. The GATA6 gene encodes a transcription factor (GATA-binding protein 6) that is essential for regulating cellular differentiation and organogenesis, expressing during em-

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bryogenesis in organs derived from the endoderm and mesoderm (heart, pancreas, intestines, lungs, and liver). GATA6 mutations are more frequently detected in premature infants (9%) than in term infants (2%) [9]. According to one study, term and late preterm infants born at a gestational age >32 weeks are more likely to have a monogenic cause of their diabetes than very premature children born at <32 weeks of gestation.

GATA6 syndrome is associated with pancreatic agenesis/hypoplasia and diabetes, along with congenital heart anomalies and several types of cancer. Monogenic diabetes caused by mutations in the GATA6 gene was long considered as neonatal diabetes. However, multiple research findings and analyses have demonstrated a variable spectrum of diabetes: neonatal (72.7%), childhood onset (20%), and adult onset (7.5%), with 83.5% of patients exhibiting abnormal pancreatic development [10].

Pancreatic manifestations of GATA6 include: hypoplasia/agenesis of the pancreas, malabsorption diarrhea, severe dehydration, intrauterine growth retardation, and postnatal physical developmental deficits. Extrapancreatic manifestations present as congenital heart defects (in 90% – ventricular septal defect), biliary tract anomalies (in 17% – agenesis of the gallbladder), concomitant/endocrine dysfunctions (10.2% hypothyroidism), neurocognitive disorders (38%), intestinal development anomalies (21%), and celiac disease (1%) [11]. The initial assessment of children suspected of having NDM includes:

- Laboratory evaluation (serum and urinary glucose, ketone bodies in urine, C-peptide, insulin),
- For infants with transient neonatal diabetes (TNDM), monitoring glycemia is more predictable through glycated albumin, which reflects glucose levels over the past 2-4 weeks,
- HbA1c is indicated for children > 6 months,
- Ultrasound of internal organs (presence/absence of the pancreas),
- CT of internal organs (detects pancreatic malformations),
- For patients diagnosed between 6 and 12 months, testing for islet antibodies is recommended, as most patients in this age group have type 1 diabetes.
- Genetic testing is an absolute indication for patients presenting with extreme acute hyperglycemia (serum glucose >1008 mg/dl) without an identified cause, regardless of progression over time. The latest guidelines recommend that all patients diagnosed with diabetes within the first 6 months of life undergo immediate molecular genetic testing to define their subtype of monogenic neonatal diabetes [12,13].

The principles of treatment for GATA6 syndrome include: insulin therapy; pancreatic enzyme replacement therapy; administration of fat-soluble vitamins (vitamins A, D, E, K); permanent dietary monitoring; and treatment and monitoring of associated conditions [14,15].

CLINICAL CASE PRESENTATION

History of the disease

The child has been considered ill from the first days of life when he was diagnosed with persistent hyperglycemia (306-504 mg/dl), simultaneously showing weight loss. On the 5th day of life, he was transferred to the Intensive Care and Reanimation Unit (ICU) of the municipal hospital in serious condition, caused by dehydration, hypotrophy, hyperbilirubinemia, and anemia. At the age of 20 days, he was redirected by the Aviasan service to the Mother and Child Institute for examination and treatment, being admitted to the ICU. Concurrently, he exhibited bowel disorders for which he was investigated and was found to have data indicating exocrine pancreatic insufficiency with significantly low elastase in feces (<15 μg/g). With insulin treatment, a positive dynamic was observed: the child gained weight consistently.

Life history

The child is from pregnancy III, birth II. The pregnancy proceeded with gestosis and a threat of miscarriage in the second trimester. Physiological birth at a gestational age of 35 weeks, with a weight of 1650 g, height 41 cm, head circumference 30 cm, chest circumference 24 cm, Apgar score 7/7 points. The anhydrous period was 4h 30min. He has not been vaccinated. He was breastfed for the first 2 months, then fed with lactose-free NAN formula. At the first year of life, his physical development was delayed, with insufficient weight gain - 300-200 g per month. He underwent surgical intervention for atrial septal defect repair and CAP ligation, with positive results. At the age of 2 years, he suffered from bilateral pneumonia with severe progression, complicated by right upper lobe atelectasis and bilateral exudative pleurisy.

The family history is burdened as the patient's cousin suffers from cystic fibrosis (heterozygous for the CFTR F508del mutation).

Objective examination

Examination performed at the age of 5 years. General condition moderately severe, in the context of underlying pathology, determined by metabolic imbalance, with periodic thirst, polyuria, fatigue,

and emotional lability. Physical development is deficient: body weight 14.5 kg (<P3; -2 SD), height 105 cm (<P3; -2 SD), BMI = 13.2 kg/m² (P10; -2 SD). Skin is pale pink, cold, and diffusely dry. Subcutaneous adipose tissue is evenly distributed and poorly developed. Lymph nodes are unaltered in size and painless. The osteoarticular system shows no visible pathological deformities. Movements are full in volume. Muscle strength is moderately diminished.

Respiratory system. Nasal breathing is free, pharyngeal isthmus is clear. The chest is symmetrical, both hemithoraxes participate in the respiratory act. Percussion elicits clear bilateral pulmonary sounds. Auscultation reveals bilateral vesicular murmur in the lungs; no rales are detected. Respiratory rate (FR) is 22/min. SpO_2 is 98%.

Cardiovascular system. Pathological pulsations in the precardiac region and in the projection of the main vessels are not noted. A scar from cardiac surgery is present. Cardiac sounds are rhythmic, clear, and audible, with a medium intensity systolic murmur at the base of the heart. Heart rate is 68 beats/min, blood pressure is 80/50 mmHg.

Digestive system. Mucosa of the oral cavity is pink and clean. The tongue is slightly coated. The abdomen exhibits pronounced venous pattern, is soft, distended but accessible to palpation throughout, and is tender in the left subcostal region. Liver state: + 3.0 - 3.5 - 4.5 cm from the right costal margin, with a soft, rounded, elastic edge, moderately sensitive to palpation. Spleen + 3.0 - 3.5 - 3.0 cm from the costal margin (Figure 1).

Urogenital system. Urination is frequent, free, and painless. Giordano-Pasternatsky sign is negative bilaterally. The external genital organs are normally formed. Axillary and pubic hair is absent, corresponding to age.

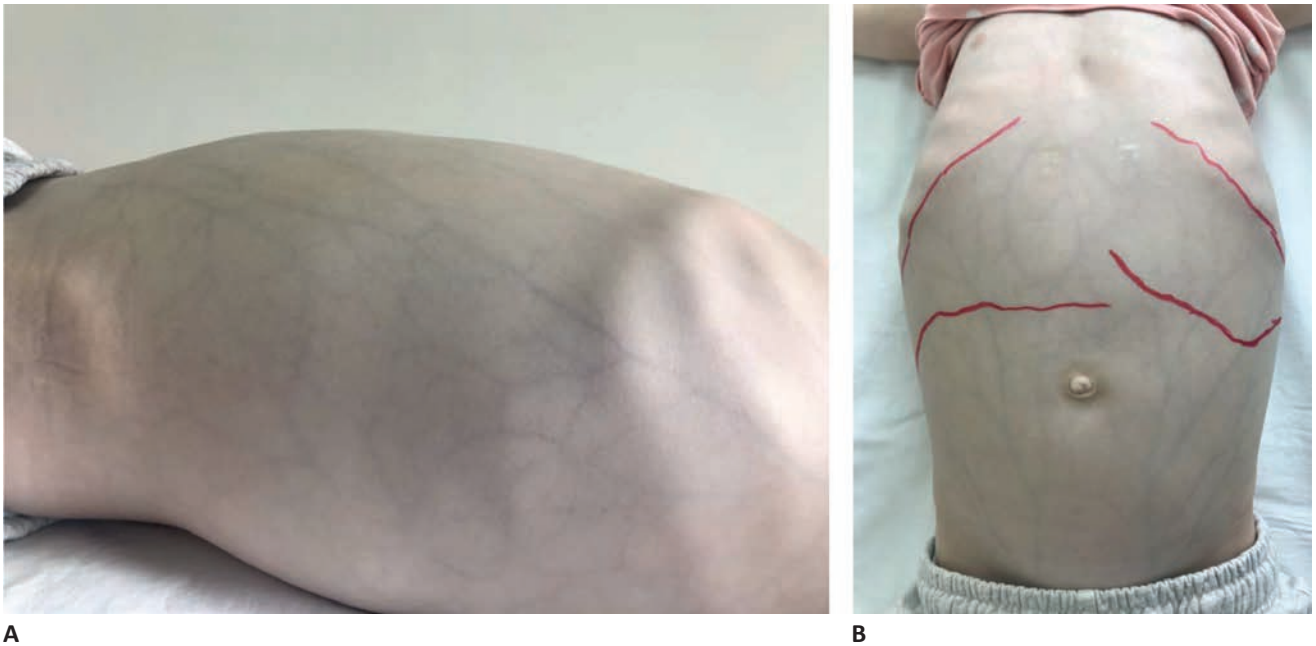
Complete blood count. Hemoglobin 105 g/l; erythrocytes 3.3 × 10^6/uL, leukocytes 5.84 × 10^9/L, neutrophils 53.9%, eosinophils 0.9%, lymphocytes 37.0%, monocytes 7.5%, ESR 7 mm/h.

Blood biochemistry analysis. Blood glucose 13.9 mmol/l, HbA1c 8.1%, B-lipoproteins 74.0 U, triglycerides 0.82 mmol/l, cholesterol 6.5 mmol/l, amylase 42 U/l, lipase 4.2 U/l, GPT 51 U/l.

Serological Investigations. HBsAg – negative, anti-hepatitis C virus antibodies - negative, anti-cytomegalovirus antibodies - negative. Anti-transglutaminase IgA antibodies positive (250 U/ml), anti-endomysium IgA (73.7 U/ml), IgG (20.5 U/ml) positive.

Electrocardiography. Sinus rhythm, regular, bradycardia, heart rate 66 beats /minute. The electric axis is deviated to the left. The electric potential of the right ventricle predominates. Disorders of repolarization processes. Partial block of the right branch of the His bundle.

Echocardiography with Doppler (after heart intervention). Levo-cardia: the presence of normal positioning of the lateral parts of the heart. Situs solitus: normal anatomical arrangement of the organs. Superior and inferior vena cava: normal course and expression. Atria: both atria have normal sizes. Interatrial septum (IAS): Intact, no evidence of anomalies or defects. Tricuspid valve (TV): Mild physiological insufficiency without clinical relevance; blood flow is dependent on respiration and



A B

FIGURE 1. Appearance of the abdomen (A) and dimensions of the liver (B) in a patient with DZN

is laminar. Right ventricle (RV): normal size and good function. Pulmonary veins (PV): Physiological insufficiency; blood flow is laminar. Pulmonary arteries (PA): Imaging through suprasternal acoustic windows showed that the right pulmonary artery is normal, but the left pulmonary artery is narrowed (5 mm) with accelerated blood flow (3m/s) and a pressure gradient of 36 mm Hg. There is no persistent patent ductus arteriosus (PDA). Mitral valve (MV): Intact function with laminar flow dynamics; the E>A pattern indicates normal diastolic function. Left ventricle (LV): Good function and usual size, with an left ventricular end-diastolic dimension (LVEDD) of 29 mm and a fractional shortening (FS) of 43%. Aortic valve (AoV): tricuspid valve, competent with laminar outflow. Coronary arteries: normal origin and unremarkable appearance. Aortic arch: unremarkable with laminar flow. Interventricular septum (IVS): Intact, no anomalies. In summary, there are some physiological insufficiencies in the tricuspid and pulmonary valves, but there are no significant structural anomalies or dysfunction in the remaining chambers or valves of the heart. The results indicate overall normal cardiac function, except for the somewhat narrowed left pulmonary artery and the increased flow gradient.

Computed tomography: The liver has a normal shape, clear contours, homogeneous density of 50-70 UH, dimensions: 15.0 × 22.0 × 13.0 cm. No heterogeneous formations or pathological accumulations of contrasting substance are present. The intrahepatic and extrahepatic bile ducts are not dilated, and the common bile duct measures 9.0 mm. The gallbladder and pancreas are not detected. The spleen has a homogeneous structure, density of 39-40 UH, no heterogeneous foci are present, and it is not enlarged in size. The adrenal glands have a normal shape and dimensions, density of 29 UH, thickness of the legs is 2.9 mm, and no formations are present. The kidneys have normal shape, position, and dimensions; the cortico-medullary layer is well-differentiated, and the renal pelvis and calyces system is not dilated. The ureters follow a normal course, are patent, and are not dilated. The secretory and excretory functions are not altered. Enlarged lymph nodes or intra-abdominal collections were not detected. Summary: CT imaging findings suggest agenesis of the pancreas and gallbladder (Figure 2).

Molecular-genetic tests

a) The "de novo" mutation (NM_005257.5:c.(1135+1_1136-1) _1620 +1_1621-1)del.p) was detected in a heterozygous state, with pathogenic expression, located on chromosome 18 (Chr18:g.(19756799-?)_(19763112+?) (Table 1).
b) The HLA DQ2 haplotype, which determines the development of gluten intolerance, was detected.
c) Investigated for CFTR 508del, the result was negative.

Clinical Diagnosis

Permanent neonatal genetic diabetes associated with the GATA-6 gene, severe form, unbalanced (KB60.2). Agenesis of pancreas (Q45.0). Agenesis of the gallbladder (Q44.0). Congenital heart malformation, operated (DSA plasty, CAP ligation) (Q21.0). Left branch stenosis of the pulmonary artery (Q25.6). Tricuspid valve insufficiency grade I (BB61). Heart

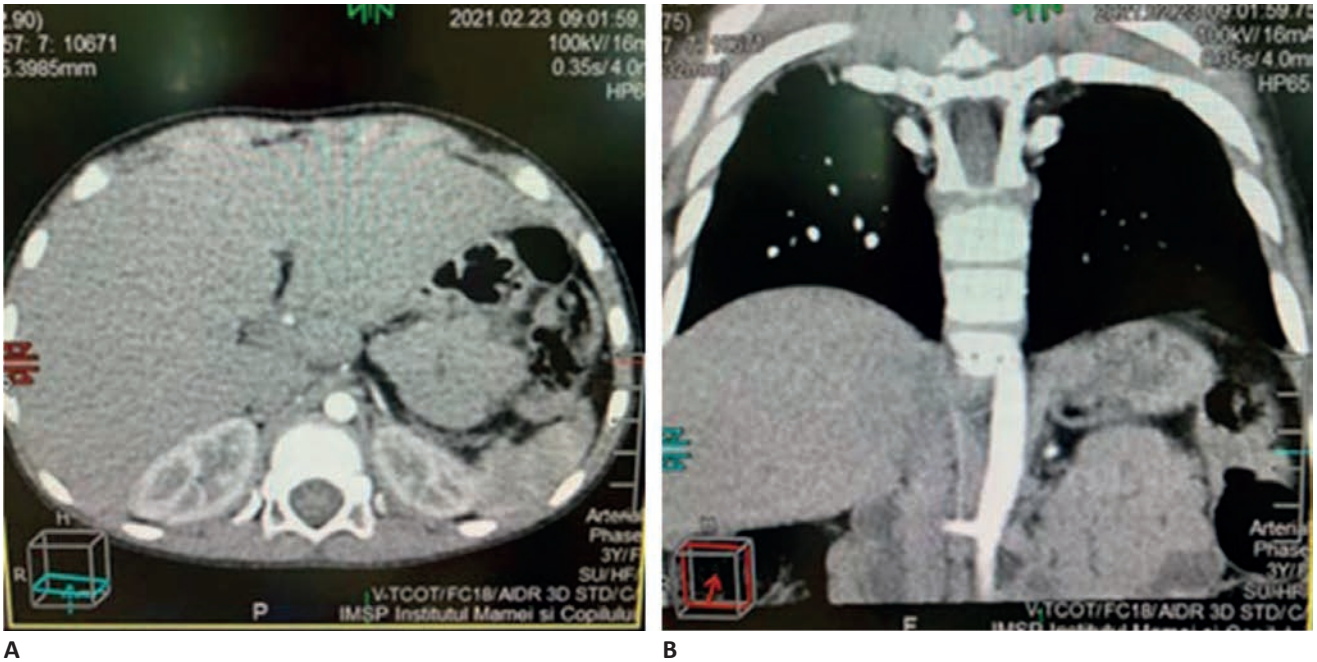
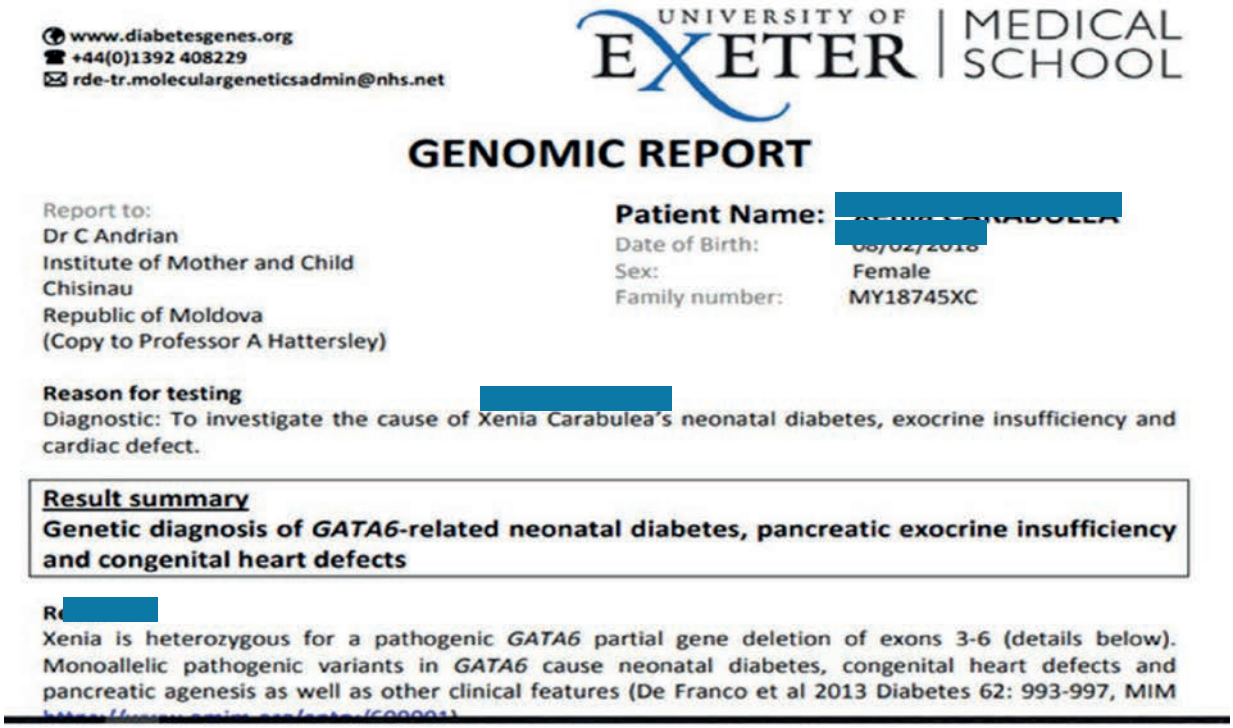


FIGURE 2. Imagistic CT data for pancreatic (A) and gallbladder agenesis (B)

TABLE 1. Result of the molecular-genetic test for diagnosing GATA6 syndrome



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GENOMIC REPORT

Report to:
Dr C Andrian
Institute of Mother and Child
Chisinau
Republic of Moldova
(Copy to Professor A Hattersley)

Patient Name: [redacted]
Date of Birth: [redacted]
Sex: Female
Family number: MY18745XC

Reason for testing
Diagnostic: To investigate the cause of Xenia Carabulea's neonatal diabetes, exocrine insufficiency and cardiac defect.

Result summary
Genetic diagnosis of *GATA6*-related neonatal diabetes, pancreatic exocrine insufficiency and congenital heart defects

Re[redacted]
Xenia is heterozygous for a pathogenic *GATA6* partial gene deletion of exons 3-6 (details below). Monoallelic pathogenic variants in *GATA6* cause neonatal diabetes, congenital heart defects and pancreatic agenesis as well as other clinical features (De Franco et al 2013 Diabetes 62: 993-997, MIM

Gene	Zygosity	Inheritance	HGVS description	Location: GRh37(hg19)	Classification
GATA6	Heterozygous	De novo	NM_005257.5:c.(1135+1_1136-1)_1620 +1_1621-1)del.p	Chr18:g.(19756799-?)_(19763112+?)	pathogenic

failure CF I-II NYHA/Ross, with preserved LVEF, stage B (BD11.0). Cardiac rhythm disturbances. Sinus bradycardia (R00.1). Exocrine pancreatic insufficiency (K86.8.0). Gluten intolerance (DA95). Height-weight retardation (R62.8). Protein-calorie malnutrition grade II-III (E44). Iron deficiency anemia grade I (3A00).

DISCUSSIONS

The patient had a complex clinical picture with multisystem involvement, which proved to be very challenging from a diagnostic standpoint. Neonatal diabetes was suspected due to persistent hyperglycemia that appeared during the neonatal period. The child's severe condition, manifested by hyperglycemia, weight loss, diarrhea with steatorrhea, hyperbilirubinemia, and iron deficiency anemia, justified the patient's admission to the RTI department for diagnosis, treatment, and monitoring.

At the Mother and Child Institute clinic, following rigorous instrumental investigations and consultations with specialists, the diagnosis of "congenital heart defect" was established, specifically; atrial septal defect and pulmonary artery stenosis, which were surgically corrected at the age of 1.5 years.

Considering the family history burdened with cystic fibrosis in relatives and the presence of steatorrhea in the patient, a genetic test for the CFTR 508del mutation was performed, which turned out to be negative. Concurrently, the patient was serum tested for gluten intolerance, with positive results in this case.

Suspicion of GATA6 syndrome arose when agenesis of the pancreas and gallbladder was detected during the computerized CT investigation. Molecular genetic testing confirmed the GATA6 syndrome, as a "de novo" mutation was found in the heterozygous state, with pathogenic expression located on chromosome 18.

The treatment of neonatal diabetes in our patient was adjusted and optimized through insulin pump therapy starting at the age of 1 year. Insulin therapy was readjusted during hospitalization. Overall, good blood glucose control was achieved by adhering to all diabetic rules and consistent therapy.

The prognosis for patients with GATA6 is difficult to predict in the long term. It largely depends on the severity of signs and symptoms, as well as associated complications. Establishing an early diagnosis and initiating appropriate treatment positively influences the patient's outcome. Maintaining normoglycemia is the target in managing neonatal diabetes [16].

CONCLUSIONS

1. Neonatal diabetes mellitus should be suspected in cases of persistent insulin-dependent hyperglycemia lasting more than 7-10 days.
2. It is important to distinguish neonatal monogenic diabetes from other causes of hyperglycemia in newborns.
3. Molecular-genetic analysis of this patient group should be considered mandatory. This can monitor other associated problems and syndromes, as well as screen family members.
4. Timely administration of insulin replacement therapy and pancreatic enzymes ensures a favorable prognosis in cases of pancreatic agenesis, thus reducing neonatal mortality caused by this severe diagnosis.

Ethical statement: This case report follows the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Informed consent: The patient's guardian agreed to participate and signed an informed consent form for having their data published in a journal article.

Author's contributions:
Galina Gorbunov: Conceptualization, methodology, software, validation, formal analysis, writing—original draft preparation, writing—review and editing, visualization, supervision, project administration
Marina Vasiliţa: Investigation
Andrian Chiriac: Resources, data curation
All authors have read and agreed to the published version of the manuscript.

Conflict of Interest: The authors declare no financial or personal relationships that might bias the content of this work.

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