

TYROSINEMIA TYPE 1: A CASE REPORT

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ABSTRACT

Background. Hereditary Tyrosinemia Type 1 (HT1) is an orphan disease belonging to the group of amino acid metabolism disorders, with an autosomal recessive pattern of inheritance. It is caused by a mutation in the FAH gene, which encodes the enzyme fumarylacetoacetate hydrolase. The clinical presentation is polymorphic. Diagnosis is based on the detection of specific metabolites in biological samples and molecular genetic testing. Early diagnosis determines the effectiveness of therapy and the prognosis of the disease.

Clinical case description. We present a clinical case of early detection of HT1 in a female newborn through expanded neonatal screening. The clinical picture was characterized by hepatomegaly, coagulopathy, and specific biomarkers, including elevated levels of succinylacetone in the blood. This finding served as the basis for immediate initiation of nitisinone therapy and an individually calculated low protein diet supplemented with a specialized amino acid mixture. Molecular genetic testing confirmed the diagnosis: a previously described pathogenic nucleotide sequence variant, chr15:80181069G>C in the FAH gene in a homo/hemizygous state, was identified. This variant leads to a missense substitution c.1090G>C, p.(Glu364Gln). During the follow up period, the patient has shown a favorable course of the disease.

Conclusion. Early diagnosis of HT1 based on specific succinylacetone screening and timely initiation of pathogenetic therapy combined with dietary management ensure a favorable prognosis for the disease.

Keywords: hereditary tyrosinemia type 1 (HT1), newborn infants, inherited metabolic disorders, clinical case

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ТИРОЗИНЕМИЯ 1 ТИПА: ОПИСАНИЕ КЛИНИЧЕСКОГО СЛУЧАЯ

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РЕЗЮМЕ

Наследственная тирозинемия 1 типа (НТ1) — орфанное заболевание из группы нарушений метаболизма аминокислот с аутосомно-рецессивным типом наследования, обусловленная мутацией в гене FAH, который кодирует фермент фумарилацетоацетатгидролазу. Клиническая картина полиморфна. Диагностика заболевания основывается на выявлении специфических метаболитов в биологическом материале и молекулярно-генетическом исследовании. Ранняя диагностика определяет эффективность терапии и прогноз заболевания.

Описание клинического случая. Представлен клинический случай раннего выявления НТ1 у девочки в рамках расширенного неонатального скрининга, клиническая картина характеризовалась гепатомегалией, коагулопатией и специфическими маркерами – повышение сукцинилацетона в крови, что послужило основанием для начала терапии нитизиноном и индивидуально рассчитанной низкобелковой диеты со специализированной аминокислотной смесью. Молекулярно-генетическое исследование подтвердило диагноз: выявлен описанный ранее как патогенный вариант нуклеотидной последовательности chr15:80181069G>C в гене FAH в гомо-/гемизиготном состоянии, приводящий к миссенс-замене с.1090G>C, p.(Glu364Gln). За время наблюдения за пациентом отмечается благоприятное течение заболевания. **Заключение.** Ранняя диагностика НТ1 на основе специфического скрининга сукцинилацетона и своевременное начало патогенетической терапии в сочетании с диетотерапией обеспечивают благоприятный прогноз заболевания.

Ключевые слова: наследственная тирозинемия 1 типа, новорожденные дети, наследственные болезни обмена веществ, клинический случай

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Hereditary tyrosinemia type 1, also known as hepatorenal tyrosinemia (HT1) (OMIM 276700), is an orphan disease belonging to the group of amino acid metabolic disorders with an autosomal recessive mode of inheritance. Its prevalence averages 1 per 100,000–200,000 live births, with significant variability reflecting demographic history and population genetics. The highest prevalence worldwide is observed in Quebec, Canada (1:1,846 live births). In Russia, marked regional heterogeneity has been identified with the highest incidence in the Chechen Republic (1:16,020) [1]. Meanwhile, the epidemiological profile of East Asia remains poorly characterized in literature.

The *FAH* gene responsible for the development of this disorder is mapped to the chromosomal locus 15q23–q25. Its genomic organization spans a region of 30–35 kb and includes 14 coding exons. To date, more than 100 pathogenic variants of the *FAH* gene associated with HT1 have been described [2]. The global literature shows a clear geographical distribution of key pathogenic alleles. The splicing variant c.1062+5G>A is predominant in Northern Europe and the US, while c.554-1G>T mutation is characteristic of Central and Eastern Europe [3]. In East Asia, variants c.1100G>A and c.192G>T are more common. Studies on the Russian cohort revealed pronounced ethnic stratification of pathogenic variants. The c.1025C>T allele is prevalent among Chechen patients, while missense substitution c.1090G>C (p.E364Q) is frequent in Buryats, Nents, and Yakuts [4, 5].

The pathogenesis of the disease is based on a deficiency of the enzyme fumarylacetoacetate hydrolase (FAH), encoded by the *FAH* gene (15q25.1), leading to the accumulation of the abnormal metabolite succinylacetone in the body [6]. FAH deficiency causes accumulation of maleylacetoacetate, which with preserved maleylacetoacetate isomerase activity undergoes non-enzymatic

reduction to succinylacetone, exhibiting pronounced hepatotoxicity and nephrotoxicity. The key mechanism for its pathological action is potent inhibition of δ -aminolevulinic acid dehydratase, leading to the accumulation of δ -aminolevulinic acid, causing porphyria-like crises, manifested clinically as neurological disorders and jaundice. At the same time, intracellular transport is disrupted and the activity of tyrosine catabolic enzymes is modulated, exacerbating multi-organ involvement (Figure).

HT1 is characterized by high mortality in the absence of timely therapy: without treatment, up to 90 % of patients with the acute form die before the age of 10 from liver failure or hepatocellular carcinoma. There are two forms of the disease: acute and chronic. They differ in onset age and rate of progression. Acute form is the most common (75 %) and presents in neonatal period or first months of life with constellation of symptoms including hepatopathy (jaundice, hepatomegaly, coagulopathy), metabolic decompensation (vomiting, dehydration, failure to thrive), neurological disorders (hypotonia), and a characteristic (cabbage-like) odor. Intercurrent infections increase risk of acute hepatic crisis with ascites and bleeding. Without treatment prognosis is fatal due to liver cirrhosis or hepatocellular carcinoma before 1 year age. The chronic form is characterized by a delayed onset, an indolent course, and the predominance of neurological (polyneuropathy) and cardiac (hypertrophic cardiomyopathy) manifestations. The onset occurs in older children and adolescents [8].

The gold standard for early diagnosis of hereditary tyrosinemia type 1 is the measurement of succinylacetone in dried blood spots using tandem mass spectrometry (TMS/MS-MS). Succinylacetone is a highly specific and pathognomonic metabolite absent in healthy newborns. It accumulates exclusively in patients with fumarylacetoacetate

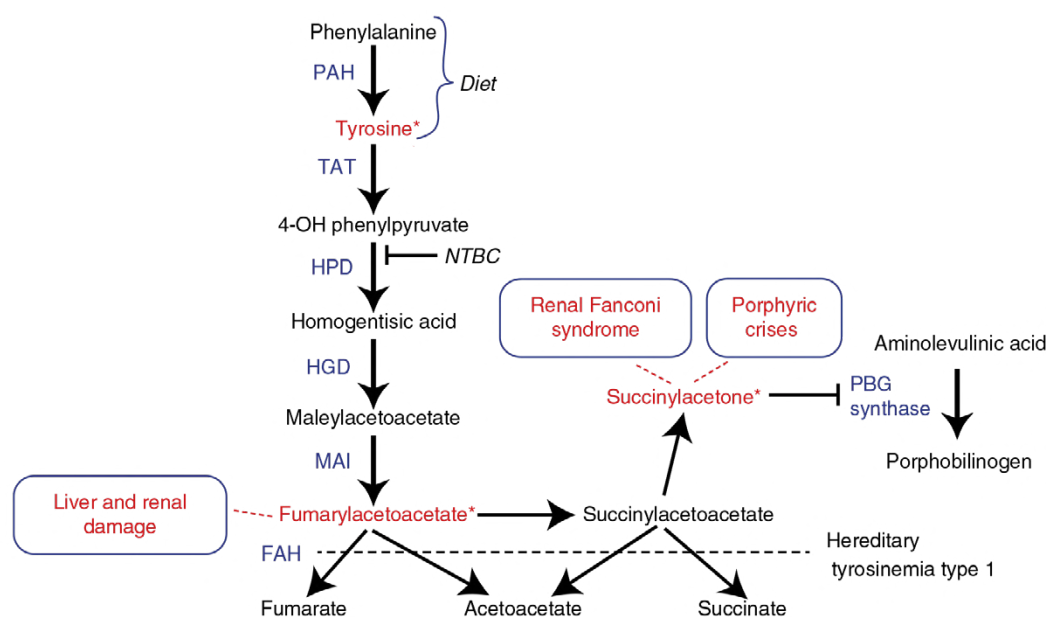


FIG.
Tyrosine metabolism disorders observed in tyrosinemia type I [7]

hydrolase deficiency. Its detection in blood collected on days 3–5 of life provides diagnostic sensitivity and specificity exceeding 95 %. This allows verification of the diagnosis before the development of clinical manifestations of hepatic and renal involvement [9, 10].

The mainstay of treatment is dietary therapy, with restriction of tyrosine and phenylalanine intake. Currently, nitisinone (Nitisinon (Orfadin®) (NTBC, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) is used to treat the disease. It can prevent acute hyperbilirubinemic crises and slow down the progression of liver cirrhosis and Fanconi syndrome.

In domestic literature, the main focus is on diagnostic algorithms and clinical markers for suspicion of hereditary tyrosinemia type 1 during the disease manifestation stage [1, 11]. The implementation of expanded newborn screening has changed the clinical paradigm fundamentally: in most cases, diagnosis is verified before symptoms appear. Issues related to when to start pathogenetic therapy and its long-term effect on prognosis have become more important. The question about whether preventive treatment modifies clinical outcomes and the dynamics of biochemical markers compared to therapy initiated during a metabolic crisis remains unanswered.

AIM

To describe the clinical and laboratory presentation of a patient with hereditary tyrosinemia type 1, detected at an early stage.

Informed consent. Written informed consent was obtained from the legal representative of the patient for the use of their medical data for scientific purposes.

RESULTS

Patient D., a female, was born on February 6, 2024, at the age of two years, as a result of the fourth pregnancy, which was not remarkable. The first pregnancy ended in delivery, and the sibling was healthy. The second and third pregnancies resulted in medical abortions. The parents were of Buryat ethnicity and were not consanguineous. They were somatically healthy, and their delivery was spontaneous, unassisted, and took place at 38 weeks. The birth weight was 4170 g, the length was 53 cm, and Apgar scores were 7/8. At birth, the condition was satisfactory, and the infant cried immediately after birth. Breastfeeding began on day 1 and the infant actively fed. On day 2, a sample was taken for newborn screening. On day five, the infant was discharged with a diagnosis of cerebral ischemia, grade 1 patent foramen ovale, patent ductus arteriosus, and congenital anomaly of the urinary system (left-sided pyeloectasia).

As part of the expanded newborn screening program, tandem mass spectrometry was performed at Competence Laboratory III A in Irkutsk. This revealed an elevated concentration of succinylacetone (SA) in the dried blood

spot – 3.5 $\mu\text{M}/\text{mL}$, which is above the normal range of 0–2 $\mu\text{M}/\text{mL}$. A presumptive diagnosis of tyrosinemia type 1 was made. To confirm the diagnosis, biological material was sent for DNA testing to the Bochkov Medical Genetics Research Center.

Prior to receiving the results of DNA testing, the infant was admitted to hospital on day 6 after birth. On admission, the objective findings were: weight – 3890 g (-280 g from birth weight), condition of moderate severity, skin clear and pink. On pulmonary auscultation, vesicular breathing; heart sounds rhythmic; abdomen distended; liver +1.5 cm below the costal margin, the edge smooth and elastic; spleen not palpable. Neurological status: muscle hypotonia with symmetrical and decreased reflexes, no pathological reflexes. Hemodynamics stable: heart rate 158 bpm, and saturation 99 %.

Laboratory findings on admission: the hemogram showed leukocytosis ($39.7 \times 10^9/\text{L}$; normal range $9.0\text{--}25.0 \times 10^9/\text{L}$) without a pronounced left shift.

Biochemical analysis on admission revealed hyperbilirubinemia with a predominance of direct fraction (total bilirubin – 180.3 $\mu\text{mol}/\text{L}$; normal range 0–17.0 $\mu\text{mol}/\text{L}$, direct – 11.7 $\mu\text{mol}/\text{L}$; normal range 0–5.1 $\mu\text{mol}/\text{L}$) and cholestasis syndrome: alkaline phosphatase – 2110.0 U/L (normal range 0–1076.0 U/L); CRP – 1.4 mg/L (normal range 0.2–9.0 mg/L); coagulogram showed prolongation of prothrombin time (PT – 14.5 sec; normal range 9.9–11.8 sec), decreased prothrombin index (PTI – 45.0 %; normal range 70–130 %), prolongation of activated partial thromboplastin time (APTT – 32.8 sec; normal range 22.1–28.1 sec), and elevated international normalized ratio (INR – 1.51; normal range 0.85–1.15).

Alpha-fetoprotein level – 56,000 ng/mL (normal for children aged 0 to 3 months: less than 1,000 ng/mL).

Tandem mass spectrometry: tyrosine – 307.4 $\mu\text{mol}/\text{L}$ (normal range 10–300 $\mu\text{mol}/\text{L}$); urinary succinylacetone measured by high-performance liquid chromatography with tandem mass spectrometry – 5.04 mM/mol creatinine (normal range 0–2.2 mM/mol creatinine).

In view of the identified laboratory abnormalities, the child was prescribed antibacterial therapy – ampicillin + sulbactam at a dose of 150 mg/kg/day; ursodeoxycholic acid – 30 mg/kg/day; vitamin K (1 mg intramuscularly, once); dietary therapy – a low-protein diet using a specialized amino acid formula without tyrosine and phenylalanine (Anamix Infant®) + breast milk, with a protein intake of 1.8 g/kg. The energy value of the diet is 95–145 kcal/kg/day. Pathogenetic therapy with nitisinone (NTBC, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) was started at a dose of 2 mg/kg/day until normalization of urine and blood succinylacetone levels, with subsequent dose adjustment based on expected body weight.

Sequencing performed at the Bochkov Medical Genetic Research Center identified a previously described pathogenic variant (HGMD_ID CM1619683) in exon 13 of the FAH gene (NM_000137.3). The nucleotide sequence variant chr15:80181069G>C in the FAH gene in a homo/hemizygous state leads to a missense substitution c.1090G>C,

p.(Glu364Gln), which is consistent with the diagnosis of hereditary tyrosinemia type 1 (ICD-10 code: E70.2).

During treatment, the child showed positive laboratory dynamics. The normalization of hemogram parameters was observed: leukocytes – $8.1 \times 10^9/L$ (normal range $6.6\text{--}11.2 \times 10^9/L$). Biochemical analysis showed mild residual hyperbilirubinemia with predominance of direct fraction (total bilirubin – $18.4 \mu\text{mol/L}$; normal range $0\text{--}17.0 \mu\text{mol/L}$, direct – $9.8 \mu\text{mol/L}$; normal range $0\text{--}5.1 \mu\text{mol/L}$), alkaline phosphatase – 819.0 U/L (normal range $0\text{--}1076.0 \text{ U/L}$). Coagulogram: PT – 9.9 sec (normal range 9.9–11.8 sec), PTI – 112.0 % (normal range 70–130 %), APTT – 31.1 sec (normal range 22.1–28.1 sec), INR – 0.96 (normal range 0.85–1.15). Tandem mass spectrometry: tyrosine – $193.4 \mu\text{mol/L}$ (normal range $10\text{--}300 \mu\text{mol/L}$), SA – $0.5 \mu\text{mol/L}$ (normal range $0\text{--}2 \mu\text{mol/L}$); urinary succinylacetone measured by high-performance liquid chromatography with tandem mass spectrometry – $0.6 \text{ mM/mol creatinine}$ (normal range $0\text{--}2.2 \text{ mM/mol creatinine}$).

The child was discharged from the hospital at the age of 1.5 months for outpatient follow-up. The weight gain at discharge was +1720 g, and the length increased by 11 cm. Following normalization of succinylacetone levels, the nitisinone dose was adjusted to 1 mg/kg/day, with recalculation based on the expected body weight.

During outpatient follow-ups, blood tyrosine and succinylethane concentrations are monitored every 3 months according to clinical guidelines. Succinylacetone remains within reference values, while tyrosine shows moderate elevation ($362\text{--}465 \mu\text{mol/L}$; normal range: $10\text{--}300 \mu\text{mol/L}$).

Currently, the child is 2 years old, weight – 14,260 g, height – 92 cm. The child's growth and development are appropriate for their age. Somatic and neurological status is unremarkable. The blood succinylacetone concentration is $0.2 \mu\text{mol/L}$, urinary succinylacetone is $0.44 \text{ mM/mol creatinine}$, alpha-fetoprotein is 2.3 IU/mL (less than 10.0 IU/mL), and liver function tests are within reference ranges. Ultrasound of liver and kidneys – no pathology. Serum nitisinone concentration – $17.547 \mu\text{g/mL}$ (therapeutic range $13.17\text{--}19.73 \mu\text{g/mL}$). Currently, the child is receiving nitisinone (NTBC, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) at a dose of 1 mg/kg/day. Dietary therapy – a low-protein elimination diet based on amino acid formula without tyrosine and phenylalanine (Nutrigen®20). Phenylalanine + tyrosine – 60 mg/kg/day. Energy value of the diet – 900–1800 kcal/day.

DISCUSSION

The presented case demonstrates a classic manifestation of the acute form of HT1 in the neonatal period. Key diagnostic “red flags” included:

- elevated succinylacetone levels in blood and urine;
- a combination of unconjugated and conjugated hyperbilirubinemia, with coagulopathy;
- a significant elevation of alpha-fetoprotein levels, exceeding the normal range.

Early detection of succinylacetone, a specific marker of HT1, allowed verification of the diagnosis before the development of irreversible liver changes and the timely initiation of nitisinone therapy, in accordance with clinical guidelines, which recommend that nitisinone initiation should not be delayed pending genetic confirmation when the clinical and biochemical picture is consistent with a positive succinylacetone test.

Dietary therapy remains an essential component of comprehensive management of HT1 patients, acting synergistically with pathogenetic nitisinone therapy. Current international and Russian clinical guidelines recommend individualized calculated restriction of natural protein intake to 20–30 % of the age-specific norm, supplemented with essential amino acids, vitamins, and trace elements using specialized formulas that do not contain phenylalanine and tyrosine [1, 7]. The key principle is not complete protein exclusion, but rather precise dosing of the “natural” protein intake, followed by supplementation with amino acid formulations. Regular monitoring every 3 months, depending on age and stability of parameters, allows for timely dietary adjustments, preventing both metabolic decompensations and iatrogenic protein-energy malnutrition. Restriction of traditional sources of complete protein increases the risk of deficiencies in calcium, iron, zinc, and vitamins B12 and D, necessitating mandatory nutraceutical support, regular monitoring of biochemical markers, and the involvement of a clinical dietician.

In the pathogenetic therapy of HT1, nitisinone (trade name Orfadin®) plays a key role. It was registered in the Russian Federation in 2009 (registration number LSR-007750/09). The pharmacological action of the drug is based on the inhibition of an enzyme involved in tyrosine catabolism, thereby blocking the formation and accumulation of toxic metabolites that damage hepatocytes and nephrons.

Clinical observations demonstrate that the initiation of nitisinone therapy at early stages of the disease prevents liver failure, reduces the incidence of renal involvement, and significantly decreases the risk of hepatocellular carcinoma [12–14]. International experience with nitisinone (NTBC, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) demonstrates a high prophylactic efficacy against hepatocellular carcinoma in patients with hereditary tyrosinemia type 1. When therapy is started before 2 months of age, a marked reduction in complications is observed, from 40 % in later initiation to 5 % in early initiation [15].

The prognosis for life with HT1 depends on several factors, including the timeliness of therapy initiation at the preclinical stage and adherence to treatment. This is achievable either through population-based newborn screening or through prenatal diagnosis in families with a positive history.

It is important to understand that metabolic decompensation can occur even during compliant treatment, triggered by respiratory or bacterial infections, stress, surgical interventions, fasting, or excessive physical exertion.

Therefore, caregivers should be informed about the risk of acute crises, precipitating factors, and symptoms of impending metabolic decompensation [1]. The management of HT1 patients requires a multidisciplinary approach involving pediatricians, geneticists, dietitians, and hepatologists, as well as lifelong monitoring of biochemical and instrumental parameters.

CONCLUSION

The implementation of preventive therapy from the first days of life is made possible by identifying of specific laboratory markers of the disease before the development of clinical symptoms. This is ensured by a newborn screening program. In this regard, further refinement of management algorithms for patients with hereditary tyrosinemia type 1, including validation of target biochemical parameter ranges to monitor pathogenetic treatment effectiveness and long-term surveillance, is required.

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Conflict of interest

The authors declare no conflict of interest.

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