

A clinical case in pediatric practice: mitochondrial DNA depletion syndrome, type 2 (myopathic form)

Anastasia V. Batyarkina¹, Bogdan S. Roy¹, Nikolay A. Dorokhov¹, Dmitry G. Polukhin², Danil V. Osintsev³, Dinara O. Akhmetzhanova⁴

¹ Altai State Medical University of the Ministry of Health of the Russian Federation,

40 Lenin Avenue, 62 Chkalova Street, Barnaul, 656038, Russia;

² Children's City Clinical Hospital No. 7, Barnaul, 230-a Severo-Zapadnaya Street, Barnaul, 656050, Russia;

³ Siberian State Medical University of the Ministry of Health of the Russian Federation, 2 Moskovsky Trakt, Tomsk, 634050, Russia;

⁴ Semey Medical University, 103 Abaya Street, Semey, 071400, Republic of Kazakhstan

Abstract. The paper discusses the diagnosis and treatment of mitochondrial DNA depletion syndrome (MDS), which is associated with a defect in the thymidine kinase 2 (TK2) gene. Despite the expansion of neonatal screening (up to 36 diseases, with plans to increase it to 62), the detection of MDS requires expensive whole-genome sequencing and is not yet available on a large scale. A case of a girl with TC-2-associated mitochondrial myopathy is described: the disease manifested itself at 9 months with weakness of the limbs and regression of motor skills, complicated by pneumonia, respiratory failure and cardiomyopathy. The diagnosis was confirmed genetically. The patient received therapy with deoxythymidine and deoxycytidine — the condition stabilized, new skills appeared. Long-term follow-up showed a decrease in the frequency of pneumonia, improvement of tests and a decrease in dependence on respiratory support. The importance of early genetic diagnosis and access to treatment is emphasized; research centers and telemedicine can help with this.

Keywords: mitochondrial myopathy, TK2 gene, thymidine, deoxycytidine, mitochondrial DNA depletion syndrome

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Introduction. The problem of diagnosing hereditary diseases has been partially solved by the introduction of expanded neonatal screening, which currently includes 36 diseases and is planned to be expanded to 62 diseases in the future.

The detection of a number of hereditary diseases, including mitochondrial depletion syndrome, requires the use of expensive methods related to whole-genome sequencing, and currently cannot be organized on a screening basis.

Mitochondrial DNA depletion syndrome is a heterogeneous group of genetically determined diseases that are based on a decrease in the number of functionally active copies of mitochondrial and/or regulatory nuclear DNA genes [1]. The result of such a genetic defect is a disruption of mitochondrial function, which is reflected in damage to target organs and cells, whose bioenergetic processes are most actively involved in the expression of defective genes [2].

Due to the variety of neurological symptoms, there is a high risk of late diagnosis of these conditions and possible associated consequences, so the true prevalence of mitochondrial dysfunction syndrome remains unknown. In addition to neurological deficits, hypertrophic cardiomyopathy may be the "debut" symptom, which has a wide differential diag-

nostic list, including amyloidosis [3]. According to available data, by 2018, 108 patients worldwide had been diagnosed with mitochondrial DNA depletion syndrome associated with mitochondrial thymidine kinase deficiency [4].

Depending on the affected gene, the result is encephalomyopathic, myopathic, neurogastrointestinal encephalopathy, encephalomyopathic, or hepatocerebral forms [2].

In the case of type 2 thymidine kinase (TK-2, mitochondrial) gene defect, there is a decrease in the production of thymidine triphosphate, one of the components of DNA, including mitochondrial DNA, which leads to a disruption of the replication process and a decrease in the number of functionally active copies of mitochondrial genes, resulting in a disruption of all mitochondrial functions [5]. Clinically and pathomorphologically, more pronounced damage in this form of the disease is observed within the striated muscles in the form of myopathy [2]. Based on the timing of manifestation, there are early (before 1 year), childhood (from 1 year to 12 years), and late (after 12 years) forms; the extent of the phenotype, as well as the prognosis, correlates with the timing of manifestation. The early form is characterized by a combination of skeletal muscle damage (hypotonia, regression of skills) with extraskele-

tal muscle manifestations (dysphagia, chronic respiratory failure, esophageal reflux with the development of aspiration pneumonia, cardiomyopathy) and an unfavorable prognosis, while the late form is oligosymptomatic (proximal myopathy of the flexors, neck, and facial muscles; the diaphragm may be involved, and dysphagia and dysarthria are less common) and has a more favorable prognosis [5]. Given the involvement of the diaphragm and the potential development of gastroesophageal reflux [5], aspiration pneumonia, including recurrent forms, is a common complication [6]. The diagnosis of TK-2-associated mitochondrial depletion is based on clinically significant myopathy with regression of motor skills, laboratory-confirmed lactic acidosis, and increased blood creatine kinase activity, but the diagnosis can only be confirmed using molecular genetic methods, such as whole-genome sequencing [2].

The National Center for Neuromuscular Diseases in Spain has described the experience of oral replacement therapy with deoxythymidine (dT) and deoxythymidine monophosphate (dTMP). Given the permeability of the mitochondrial membrane for both metabolites, it is possible to compensate for the deficiency of mitochondrial thymidine kinase activity by boosting the function of cytosolic thymidine kinase through the exogenous

administration of dT and/or dTMP. When dT and dTMP are administered orally, not only is the progression of the disease halted, but there is also a clinically significant regression [4].

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Clinical case: a child (a girl) at the age of 1 year was admitted to a level 2 medical institution for inpatient treatment at the direction of a district neurologist with complaints of weakness in the legs, maintaining the tilt of the head to the left shoulder, the child stopped sitting, getting up on all fours.

Anamnesis. A child from 2 pregnancy, 1 birth. Pregnancy on the background of chronic arterial hypertension. Giving birth at 38 weeks, naturally. Birth weight 2800 g. Height 49 cm. Apgar 7-8 points. The condition from birth is satisfactory, according to neurosonoscopy, there is a moderate increase in the echogenicity of the periventricular zones. At the age of 28 days, she was examined by a neurologist at her place of residence. The diagnosis was made: the consequences of perinatal encephalopathy (PEP) of hypoxic-ischemic origin. Syndrome of increased neuro-reflex excitability. She was observed by a neurologist on an outpatient basis once every 2-3 months. Up to 9 months, the girl developed in age: she held her head from 3 months, turned over on her stomach at 4 months, sat down at 7 months, got on all fours at 9 months.

The disease first appeared at the age of 9 months in the summer period with the manifestation of intoxication syndrome (fever up to 38.3), in which there was an increasing weakness in the lower extremities for 3 days. After 2 weeks, the condition worsened, the weakness of the lower extremities increased, the torticollis to the left, the child stopped sitting, getting up on all fours.

At the age of 11 months, he underwent treatment with an osteopath. At the beginning of treatment, there was a positive trend, she began to turn her head in different directions, but the tilt of the head remained. At the age of 1, she was examined by a neurologist at her place of residence, and was diagnosed with the effects of PEP, hypoxic-ischemic genesis. Muscular hypotension syndrome. Neurogenic torticollis.

At the age of 1 year and 1 year and 2 months, she received treatment in a pediatric neurological hospital. As a result of the examination and treatment, a diagnosis was made: the consequences of AEP,

combined genesis, motor disorders syndrome (muscular hypotension). Delayed motor and speech development. Neurogenic torticollis. Treatment was carried out, without objective improvement.

She was consulted and examined by a geneticist at the age of 1 year and 2 months. The diagnosis was made: the consequences of perinatal encephalopathy, hypoxic-ischemic genesis. Muscular hypotension syndrome. Neurogenic torticollis. There was no data on hereditary metabolism according to the results of the examination. Repeated consultation at the age of 1 year and 5 months. Exclude spinal muscular atrophy (SMA).

At the age of 1 year and 7 months, she was examined at the Scientific Research Clinical Institute, Moscow. According to the results of which it was concluded: given the onset of the disease at the age of 6-8 months, the typical clinical picture of the disease in the form of a predominant lesion of the neck and upper shoulder girdle muscles with high levels of CPK, rapid progression and early development of respiratory disorders, the child is most likely to have a diagnosis of mitochondrial DNA depletion syndrome (myopathic type) associated with mutations in the TK2 gene. Differential diagnosis should be performed with Brown-Vialetto-Van Laere syndrome (BVVLS) (C20orf54). Exomic sequencing was initiated to clarify the diagnosis. If the result is negative, genome-wide sequencing; non-obstructive hypertrophic cardiomyopathy.

From May to July 2023, at the age of 1 year and 7 months, she received inpatient treatment with a diagnosis of severe aspiration pneumonia, respiratory failure of 3 degree. hypertrophic cardiomyopathy, non-obstructive form. Cardiac arrhythmia: supraventricular paroxysmal tachycardia, post-seizure period, circulatory insufficiency of 2A degree. Mitochondrial DNA depletion syndrome. Neurodegenerative disease cannot be ruled out.

She was in the intensive care unit on the respiratory support of a ventilator for 19 days. After her condition stabilized, she was transferred to the department for further treatment, with continued respiratory support and monitoring of vital functions. During the treatment in the department, the child was on a ventilator for 24 days (06/17/2023–07/11/2023). After recovery, she was discharged with recommendations, and transferred to a noninvasive ventilation device with mandatory use at night, due to a decrease in saturation.

From September to December 2023, at the age of 1 year 10 months – 2 years 2 months, the girl suffered 3 pneumonias:

severe bilateral pneumonia, complicated by respiratory failure of 2-3 degree; severe bilateral polysegmental pneumonia, complicated by respiratory failure of 2-3 degree; Severe right-sided upper lobar pneumonia, complicated by respiratory failure of 2-3 degree.

During the examination in December 2023: in the clinical blood test, hemoglobin is within the normal range, normochromia, normocytosis. Neutrophilosis is relative, ESR is normal. In the biochemical analysis of blood: ALT 156 Units / l, AsAT 181 Units/l, Lactate dehydrogenase 835 Units/l — the dynamics from May 2023 is stable, unchanged.

Ultrasound examination of the thymus gland – the volume of the thymus gland is not enlarged. Focal changes in the right lobe of the thymus gland. Ultrasound of the internal organs shows an increase in the size of the liver.

The echocardiography – septal discharges is not detected. Signs of left ventricular myocardial hyperfunction, indicators of total left ventricular contractility: ejection fraction 77%. Slight enlargement of the right atrium. Asymmetric hypertrophic cardiomyopathy of the walls of the left ventricle is not excluded, the wall thickness does not increase dynamically. Minimal tricuspid regurgitation, heart rate tachycardia 140 beats/min.

Consultation of specialists from the National Medical Research Center (Saint Petersburg) based on the results of a molecular genetic examination: mitochondrial DNA depletion syndrome, type 2 (myopathic form). TK2-associated myopathy, infantile form. Regression of large-scale motor skills. Neurogenic dysphagia (probe feeding). Protein and energy deficiency.

It is recommended that a patient with TK2-associated myopathy receive thymidine and deoxycytidine at a therapeutic dose, according to vital indications, as the only possible treatment in this clinical case.

In December 2023, at the age of 2 years and 2 months, the intake of a specialized food product containing thymidine and a prototype of a specialized food product containing deoxycytidine began. Physical therapy regularly, kine-siotherapy.

In 2024, there were no inflammatory diseases and no pneumonia. The child was twice rehabilitated at the St. Petersburg National Medical Center (April, September 2024).

During the rehabilitation examination in September of the same year, against the background of constant long-term subsidies of deoxythymidine and de-

oxycytidine, the dynamics of treatment was positive (new neuropsychiatric development skills appeared, clinical tests improved, and the use of probe nutrition stopped). Treatment was carried out: vitamin D, metabolic therapy. Physiotherapy: aeroionotherapy, laser therapy, halo-therapy, physical therapy, hydrokinesiotherapy, verticalization. The recalculation of a special food product per kilogram of body weight was carried out.

There were no hospitalizations for inflammatory diseases in 2025. It was examined in August 2025. A 3-year-old 8-month-old girl with TK2-associated mitochondrial myopathy, her condition remained stable during hospitalization. Laboratory ALT 58.3 Units/l, AST 86.9 Units/L, creatine phosphokinase 864.9 Units/l, Lactate dehydrogenase 1592 Units/l, creatine phosphokinase-MB 123 Units/l — the dynamics from September 2024 is positive.

Polysomnography was performed, the child needs non-invasive ventilation only during intercurrent infection with respiratory failure. Correction of non-invasive ventilation and insufflator-aspirator parameters. He is discharged home in stable condition for outpatient follow-up at his place of residence. A subsidy of deoxythymidine and deoxycytidine is required.

Results and discussion. With a defect in the thymidine kinase type 2 gene (TK-2, mitochondrial), there is a decrease in the production of thymidine triphosphate, one of the components of DNA, including mitochondrial, which leads to a disruption in the replication process and a decrease in the number of functionally active copies of mitochondrial genes, as a result of which all mitochondrial func-

tions are disrupted [5]. Mitochondrial dysfunction leads to a decrease in ATP production, oxidative stress, and regular damage to the involved cells [7]. Clinically and pathomorphologically, a more pronounced lesion in this form of the disease is observed within the striated musculature in the form of myopathy [2]. In this clinical case, the development of myasthenic form was noted in a child with the first manifestations under the age of 1 year, with the development of myopathy, pneumonia and respiratory failure. This type of pathology has an unfavorable prognosis.

Conclusion. Currently, clinical material is accumulating describing various variants of the clinical manifestations of mitochondrial pathology manifested by myopathies. The diagnosis at the first stages was consistent, and pathology was suspected already at the stage before complications developed. Also, a child was one of the first in Russia to receive proper treatment, organized by the specialists of the National Medical Research Center of St. Petersburg. Thus, at the present stage, the detection of myopathies is becoming available using the capabilities of telemedicine and genetic diagnostics. The active participation of research centers and the registration of new drugs in the Russian Federation makes it possible to correct the health status of children with TC2-associated mitochondrial myopathy.

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Information about the authors: Altai State Medical University, Ministry of Health of the Russian Federation: **Anastasia V. Batyarkina** – pediatrician <https://orcid.org/0009-0009-2887-3755>; **Bogdan S. Roy** – pediatrician, <https://orcid.org/0009-0000-7686-0240>; **Nikolay A. Dorokhov** – Ph.D. (Med), Associate Professor, Head of the Department of Faculty Pediatrics, nik-dorokhov@mail.ru, <https://orcid.org/0000-0002-3823-6276>; **Dmitry G. Polukhin** – Ph.D. (Med), Head doctor, Children's City Clinical Hospital No. 7, Barnaul, <https://orcid.org/0009-0006-9465-6933>; **Danil V. Osintsev** – Resident of the Department of Medical Genetics of the Siberian State Medical University of the Ministry of Health of the Russian Federation, <https://orcid.org/0009-0006-6948-4420>; **Dinara O. Akhmetzhanova** – Ph.D. (Med), Head of the Department of Pediatrics, Associate Professor, Semey Medical University, dinara.akhmetzhanova@smu.edu.kz, <https://orcid.org/0000-0003-0000-2535>

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