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# A clinical case of X-linked adrenoleukodystrophy in a 9-year-old boy

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**ABSTRACT**

X-linked adrenoleukodystrophy belongs to peroxisomal disorders characterized by combined damage to the nervous system and adrenal glands and often leading to death. This hereditary disease results in mutations in the *ABCD1* gene, leading to ineffective β-oxidation of fatty acids following a decrease in the activity of acetyl-CoA synthetase of their long chains. Accumulation of acyl-CoA derivatives of fatty acids takes place, which affect the physicochemical properties of cell membranes.

We have described a clinical case of X-linked adrenoleukodystrophy in a 9-year-old boy with the primary manifestation of the disease at the age of 7 years and 10 months in form of enterovirus encephalitis.

Early diagnosis, prenatal screening of adrenoleukodystrophy for performing gene-specific therapy, slowing the progression of the disease, and prolonging the life of the patient with the diagnosis of a rare hereditary disease are required.

**Keywords:** X-linked adrenoleukodystrophy, adrenal insufficiency, glucocorticoids, mineralocorticoids, leukoencephalomalacia

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# Клинический случай Х-сцепленной адренолейкодистрофии у мальчика 9 лет

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**РЕЗЮМЕ**

Х-сцепленная адренолейкодистрофия относится к пероксисомным болезням, характеризуется сочетанным поражением нервной системы и надпочечников, часто приводящим к летальному исходу. Это наследственное заболевание вызывает мутации гена *ABCD1*, определяющим неэффективность β-окисления жирных кислот, в результате снижения активности ацетил-КоА синтетазы их длинных цепей. Происходит накопле-

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ние ацил-КоА-производных жирных кислот с нарушением физико-химических свойств клеточных мембран.

Нами описан клинический случай Х-сцепленной адренолейкодистрофии у мальчика 9 лет с первичной манифестацией заболевания в возрасте 7 лет 10 мес по типу энтеровирусного энцефалита.

Необходима ранняя диагностика, пренатальный скрининг для проведения специфической терапии, замедления прогрессирования заболевания, продления жизни больному с редким наследственным диагнозом.

**Ключевые слова:** Х-сцепленная адренолейкодистрофия, надпочечниковая недостаточность, глюкококортикоиды, минералокортикоиды, лейкоэнцефаломаляция

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

**Источник финансирования.** Авторы заявляют об отсутствии финансирования при проведении исследования.

**Соответствие принципам этики.** У родителей ребенка получено разрешение на публикацию анонимных данных.

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## INTRODUCTION

X-linked adrenoleukodystrophy (X-ALD) belongs to the group of hereditary metabolic diseases associated with impaired peroxisomal function. Adrenoleukodystrophy (synonyms: Zimmerling – Creutzfeldt's disease, Schilder – Addison's disease) was first described by German neuropathologists Ernst Zimmerling and Hans Gerhard Creutzfeldt in 1923. This disease is not as rare as it was previously thought to be, it occurs everywhere, and its incidence rates prevail over other peroxisomal diseases [1].

The onset of the disease is associated with mutations in the *ABCD1* gene in the terminal region of the long arm of the X chromosome (locus Xq28) [2]. This gene encodes synthesis of a transmembrane carrier protein called adrenoleukodystrophy protein (ALDP), which is located on specific cellular organelles involved in oxidation reactions, peroxisomes, and is responsible for transport and further degradation of very-long-chain fatty acids (VLCFAs) [1]. With a structural defect in the peroxisomal transport protein, it becomes functionally incapable, which leads to accumulation of toxic compounds in the tissues.

Currently, more than 2,600 *ABCD1* mutations associated with the replacement of DNA nucleotides and loss of loci have been identified [3]. Many of them cause structural changes in ALDP. Adrenoleukodystrophy develops when there is a recessive gene in the genotype (in hemizygous men) or two of its variants (in heterozygous women). X-ALD is more common in boys; in girls, the disease is asymptomatic. The incidence of adrenoleukodystrophy is 1: 17,000 live-born boys [1, 3]. The disease is manifested by two groups of clinical symptoms: primary adrenal insufficiency and demyelinating disease. These disorders are caused by mutations in the *ABCD1* gene encoding the transmembrane protein ALDP, leading to ineffective β-oxidation of fatty acids following a decrease in the activity of acetyl-CoA synthetase of their long chains. Primary adrenal insufficiency is clinically manifested through hyperpigmentation of skin folds and mucous membranes, cicatricial changes, fatigue, weight loss, dizziness, increased anxiety, chronic nausea, and vomiting. Damage to the nervous system is clinically manifested through autistic behavior, learning problems, memory loss, attention deficit, convulsive syndrome, blindness, and deafness [4].

## CLINICAL CASE

Patient S., born in 2011, was admitted to the Department of Pediatric Neurology of the City Clinical Hospital for the first time in March 2020 with complaints of weakness, lethargy, drowsiness, and disorientation.

*Anamnesis vitae and anamnesis morbi.* A boy from a second pregnancy that ended in childbirth by caesarean section at 39 weeks due to breech presentation. The first pregnancy ended in spontaneous abortion. The child was born with a weight of 3,200 g and a height of 52 cm, the Apgar score was 8 / 9.

The patient's health in early childhood was normal. The patient is vaccinated according to the calendar. The patient had rare respiratory infections and chicken pox. Until the age of 7, the parents did not report any complaints about the development of the boy. At the age of 7, mother began to notice periodic urinary incontinence in her son. According to his parents, the boy did not go to the toilet for a long time, and then he would not manage to get there in time. Therapy with oxybutynin was prescribed with appropriate water intake schedule. A positive effect was achieved.

At the age of 7 years 10 months, while the child was in a camp in Anapa, he complained of nasal congestion, single vomiting, weakness, and body temperature increase to febrile values. He was examined by a doctor, then he was isolated, an ambulance was called. Before the arrival of the ambulance, there was repeated vomiting, paroxysm developed in the form of a short-term loss of consciousness, eyes rolling back, and twitching of arms and legs. The boy was hospitalized in Krasnodar with the diagnosis of enterovirus encephalitis. He was administered carbamazepine (200 mg 3 times a day), and a positive effect was achieved.

During the autumn, the child did not feel well, he had continued weakness, lethargy, and rapid fatigability. The body temperature occasionally rose up to 37.2°C. It was recommended to consult a neurologist. Magnetic resonance imaging (MRI) of the brain was performed (December 16, 2019). According to MRI, for the first time, signs of leukoencephalomalacia were noted with symmetrical lesions in both parietal and temporal lobes, the posterior third and splenium of the corpus callosum, posterior parts of the basal ganglia, cerebral peduncles in midbrain, and pons. The boy was observed by a neurologist and an epileptologist in a local clinic. Diagnosis: "epilepsy"? Given the absence of epileptic seizures, therapy with carbamazepine was canceled. Aminophenyl-butyric acid was prescribed, which the patient took until the end of January 2020, therapy was then canceled according to the recommendation of a neurologist.

On March 28, 2020, immediately after waking up, the boy felt unwell. A single vomiting, weakness, and lethargy were noted, the child became distracted, inattentive, and disoriented in space. Paroxysm was noted in the form of fading (the patient did not respond to the mother) and eye movements. An ambulance was called. Before the arrival of the ambulance, a paroxysm developed in the form of eyes rolling back, lip twitching on the right, extended right arm and right leg. The patient did not respond to the people around him. Diazepam was administered. The child was admitted to the hospital for a comprehensive examination.

*Objective clinical examination.* An examination of the patient in the emergency room showed the following: a state of moderate severity, impaired consciousness, poor orientation in space and time, difficulties in make contact with the patient, he answered questions slowly and not always. His skin was dark and dry. The patient's skin on the elbows, in the armpits, and in the area of the buttocks was much darker (up to a chocolate brown color). In the right frontal region, a light brown spot of an irregular shape was noted. On the upper and lower extremities, 4 small (1–5 mm) light brown spots of an irregular shape were detected. A neurological examination did not reveal any changes, except for bad mood. The boy has phenotypic features: curly hair, protruding ears, deep set eyes, wide interdental spaces, dolichostenomyelia.

When the child was in the hospital, the following was revealed: hearing impairment, impaired understanding of addressed speech, and deterioration of handwriting. In the dynamics, child's space orientation became worse, and his gait became unsteady.

*Laboratory tests and instrumental diagnosis were conducted.* Blood test: ESR – 13 mm / h, other parameters were within the reference range. In the blood biochemistry test, the following parameters were increased: creatine phosphokinase 377 U / l (0–247), lactate dehydrogenase 426 U / l (0–378), glucose level was within the reference range: 4.36 mmol / l (3.3–5.9). The cortisol level was low: 01.04.2020 at 8 am – 25 nmol / l, at 10 pm – 31.5 nmol/ l; 08.04.2020 at 8 am – 12.6 nmol / l, at 10 pm – 3.2 nmol / l (reference range is 83–580 nmol / l). The level of adrenocorticotropic hormone was elevated: 127 pg / ml (with the reference range of 0–46 pg / ml).

Ultrasound examination of the thyroid gland: right lobe 24*9*9 mm, V – 0.9 cm $^3$, left lobe 28*8.5*9 mm, V – 1.0 cm $^3$. Contours were clear and even. No lesions were detected. The volume of the thyroid gland was 1.9 cm$^3$. Conclusion: thyroid hypoplasia. Electroencephalography (EEG) revealed no clear signs of impaired bioelectrical activity in the brain. Focal, paroxysmal, and epileptic activities were not registered in the study. Moderate cerebral changes with irritative zones were detected. On the basis of objective clinical examination data and the results of laboratory tests and instrumental diagnosis, the following diagnosis was made: demyelinating disease of the central nervous system, X-linked adrenoleukodystrophy.

The therapy was prescribed: valproic acid (Depakene) 180 mg 3 times a day, methylprednisolone 250 mg, thiamine 1 ml intramuscularly once every two days. The treatment had a positive effect, improving the patient's conditions, stopping psychotic states and seizures, and improving the child's mood. To carry out substitutive therapy, hydrocortisone (Cortef) was prescribed orally 10 mg per day in 3 divided doses (5 mg in the morning, 2.5 mg at lunch, 2.5 mg in the evening). The patient's discharge record was sent to the Department of Medical Genetics of the Russian Children's Clinical Hospital of Pirogov Russian National Research Medical University, to which the child was admitted in April 2020. At the time of hospitalization, the patient complained of visual and hearing impairment, lack of voluntary coordination of muscle movements, falling, dark skin, and periodic involuntary urination; the patient could not write in a straight line.

*Objective clinical examination.* Upon admission, he was in a state of moderate severity. Phenotypic features of the patient included dark skin, high forehead, wide nose bridge, wide set eyes, transverse palmar crease, and claw sign. The skin was dark without rash. The elbows and knees were hyperpigmented. There was a hyperpigmented area on the forehead on the right. Neurological status: convergence insufficiency on the right. Exotropia, more on the right. The face was slightly asymmetrical: the nasolabial fold on the right was somewhat smoothed. The patient had hearing impairment. The pharyngeal reflexes were reduced, without a clear difference in sides of the body. The patient had positive pyramidal signs. The gait was wide-based and atactic with polyneuropathy. Muscle tone – dystonia, more in the arms, D > S. Ankle jerk reflexes were reduced. The plantar reflex or Babinski sign was positive on both sides. Coordination tests: the patient tried to reach the hammer with intention tremor and slight asymmetry. Sensitivity was difficult to assess (due to hearing impairment). The patient almost did not execute commands. Speech was with dysarthria, slow and phrasal. It looked like speech and mental retardation.

*The results of the conducted tests.* Endocrine profile (29.04.2020): cortisol 82.92 nmol / l (reference value 83–580 nmol / l), adrenocorticotropic hormone (ACTH) 476 pg / ml (reference value 0–46 pg / ml). With continuous substitutive hormone therapy for a month, the level of cortisol increased, while the ACTH level remained high. The changes in the levels of blood electrolytes were the following: the level of sodium ion increased from 118 mmol / l to 138 mmol / l (reference value 135–148 mmol / l); and the level of potassium ion decreased from 4.5 mmol / l to 3.3 mmol / l (reference value 3.5–5.3 mmol / l).

Electrocardiogram (ECG) showed dysmetabolic syndrome in the myocardium (inverted T wave in V3, AVF), myocardial dystrophy. Electroneurography (27.04.2020) revealed several disorders in the muscle tone regulation: suprasegmental nature, signs of demyelination of peripheral nerves *n. Peroneus, n. Tibialis, nn. Suralis, nn. Medianus*, S > D. At that moment, no pathology of motor neuron disorders was observed at the level of cervical and lumbosacral enlargement. According to a video sleep EEG (28.04.2020), there were no data on continued regional, diffuse, and generalized epileptic activity (Table 1).

Table 1

**Dynamics in the instrumental diagnosis of the brain**

| CT (August 2019) | MRI (December 2019) | MRI (March 2020) |
|---|---|---|
| Signs of reduced density areas in the splenium of corpus callosum and the area of the posterior horns of the lateral ventricles | Leukoencephalomalacia with symmetrical lesions in both parietal, both temporal lobes, posterior third and splenium of corpus callosum, posterior basal ganglia, cerebral peduncles of the midbrain, and pons (corticospinal tracts) | Leukoencephalopathy of unknown origin. No dynamics from 12.2019 |

The disease progressed rapidly, which was manifested through an aggravation in neurological symptoms: unsteadiness when walking, visual and hearing impairment, epileptic seizures, and intellectual disorders. Widespread demyelinating process on MRI of the brain (Lewis scale 11 out of 32 points) and adrenal insufficiency were also noted.

The primary diagnosis: a degenerative disease of the nervous system from the group of peroxisomal diseases (G31.8). X-linked adrenoleukodystrophy, cerebral form (E71.3). Symptomatic epilepsy. Atactic syndrome. Cortical visual and hearing impairments. Chronic primary adrenal insufficiency. Speech and mental retardation. Secondary diagnosis: myocardial dystrophy.

The following treatment was prescribed: low-fat diet, Lorenzo's oil in the 4 : 1 ratio of oleic acid and erucic acid triglycerides. Medications included substitutive therapy with glucocorticoids and mineralocorticoids: Cortef 5 mg in the morning, 2.5 mg at lunch, 2.5 mg in the evening; Cortineff ¼ tablet twice a day in the morning and in the evening; valproic acid 3 ml three times a day. Allogeneic stem cell transplantation was not advised when the boy

was hospitalized to the Russian Children's Clinical Hospital of Pirogov Russian National Research Medical University, given the rapid progression of the disease in the patient.

After hospitalization to the Russian Children's Clinical Hospital, the child was observed by a pediatric endocrinologist and a neurologist at the place of residence. The prescribed hormonal therapy with hydrocortisone upon discharge was increased for the summer period to 30 mg / day, taking into account a progressive decrease in cortisol levels: 09.2020 – 0.7 nmol / l; 10.2020 – 3.65 nmol / l (reference value 8.7–22.4 nmol / l). The level of adrenocorticotropic hormone also remained high: 09.2020 – 458 pg / ml, 10.2020 – 390.8 pg / ml (reference value 8–57 pg / ml).

In September 2020, the child's condition worsened significantly, which required a further increase in the dose of hydrocortisone to 40 mg / day. In dynamics, the ACTH level decreased to 390.8 pg / ml, and the cortisol level increased to 3.65 nmol / l. The blood biochemistry test showed moderately pronounced changes in all parameters (Table 2).

Table 2

**Blood biochemistry test**

| Parameter | October 2020 | Reference value |
|---|---|---|
| AST, U / l | 77.8 | 0–50 |
| ALT, U / l | 54.8 | 0–50 |
| Iron, μmol / l | 5.8 | 9–21.5 |
| Chlorine, mmol / l | 90.58 | 98–107 |
| Calcium, mmol / l | 2.04 | 2.2–2.7 |
| Potassium, mmol / l | 2.88 | 3.5–5.3 |
| Sodium, mmol / l | 132.7 | 135–148 |
| Total cholesterol, mmol / l | 6.79 | 3.3–5.2 |
| Alkaline phosphatase, U / l | 49.75 | 86–315 |
| Gamma-glutamyl transferase, U / l | 23.86 | 3–22 |

## DISCUSSION

Adrenoleukodystrophy is characterized by a pronounced phenotypic polymorphism, which is associated with differences in the penetrance and expressivity of the abnormal gene. There are several forms of the disease, the development of which is determined by the time of onset, main manifestations, and the rate of aggravation. In this case, the patient had a cerebral form of the disease, the main symptoms of which are neurological disorders. According to the time of the disease onset, this is a childhood form, which occurs more often (almost in 50% of cases) [5–7]. This form generally occurs between the ages of five and ten [8].

In the present clinical case, the first moderately pronounced symptoms (enuresis) appeared at the age of 7 years, and after 10 months, more manifestations of the disease appeared. Cerebral adrenoleukodystrophy is characterized by rapid progression [9–11], which is clearly shown in the present clinical case – 8 months passed from the onset of manifestations to a severe condition.

In most patients, neuropsychiatric disorders precede signs of adrenal insufficiency. At the onset of the disease, the child was diagnosed with convulsive disorder, which required differential diagnosis with epilepsy. The child was admitted to the neurological department with complaints of impaired hearing and understanding of addressed speech, worsening of handwriting, worsened space orientation, and unsteady gait. Changes in the skin color in the form of increased pigmentation and brown spots were first detected in the hospital, earlier, parents and doctors did not pay attention to these changes. Manifestations of adrenal insufficiency were confirmed by the endocrine test. The prescription of substitutive therapy with hydrocortisone led to an improvement in hormone levels without affecting the severity of clinical manifestations. In the dynamics, there were manifestations of behavioral disorders, motor functions, thinking, and unmotivated aggression appeared.

Presymptomatic therapy is particularly important in the treatment of adrenoleukodystrophy. At this stage, diet was effective [12]. In this clinical case, diet therapy is not justified due to the already developed clinical presentation of the disease. The use of substitutive therapy with glucocorticoids and mineralocorticoids is indicated for symptoms of hypocorticism [13]. However, these drugs do not have a pathogenetic effect on the pathological process in the central nervous system [14]. Symptomatic treatment of myelopathy is conducted with neurometabolic agents, muscle relaxants, and vitamins.

The main treatment method at early stages of adrenoleukodystrophy in childhood and adolescence is allogeneic stem cell transplantation, which can stop the progression of demyelination [15, 16]. Additional methods that do not affect the mechanisms of pathology development include acupuncture, transvertebral micropolarization, massage, and exercise therapy, which are also used at initial stages of the disease to relieve spastic symptoms and muscle stiffness. Patient S., 9 years old, was diagnosed at the stage of severe clinical symptoms, so the effectiveness of the

prescribed treatment is extremely low. The prognosis is poor.

## CONCLUSION

Currently, there are no specific methods for prevention and treatment of adrenoleukodystrophy. Recommendations aimed at preventing the occurrence of this genetic pathology have been developed. Prenatal diagnosis of the disease is conducted. Treatment that is recommended at early stages of the disease involves bone marrow transplantation from a donor to a patient. Early diagnosis of adrenoleukodystrophy and comprehensive therapy significantly slow down the development and progression of the disease, prolonging the patient's life.

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