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CLINICAL CASE OF MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 5 (LEY SYNDROME)

Relevance. Diagnosis of mitochondrial pathology is a difficult practical task. The variability of clinical manifestations of mitochoric diseases is associated with high genetic heterogeneity of mitochondrial pathology. Therefore, the analysis of clinical cases of mitochondrial pathology is an urgent task for early diagnosis.

The aim of this study: to analyze a clinical case of mitochondrial complex deficiency complex I, nuclear type 5 (Ley syndrome).

The result of the study: a description of a clinical case of Ley syndrome was carried out. It is shown that the development of the disease manifested in early preschool age against the background of intercurrent disease. The disease manifested itself by metabolic disorders, degenerative signs from the nervous system, immunological changes and within 9 months led to a fatal outcome.

Conclusion. The absence of specific signs at the initial stage significantly complicates the diagnosis of the disease and leads to difficulties in diagnosis.

Keywords: Ley syndrome; "mitochondrial complex I deficiency, type 5"; NDUFS1 gene.

Relevance. Timely diagnosis of hereditary pathology remains an urgent problem in clinical medicine. Mitochondrial diseases are particularly difficult to diagnose. The genetic heterogeneity of mitochondrial diseases is extremely high, including due to mutations in genes regulating the work of mitochondria, but located in the nucleus. At the same time, there are no obvious correlations between genotype and phenotype, and a conclusion about the etiology based on a clinical or biochemical picture is difficult, and sometimes impossible [7]. In this regard, the analysis of clinical variants of mitochondrial diseases is an important and urgent task.

Introduction. Leigh syndrome (synonyms: Lee, Leigh) is a heterogeneous disease of hereditary genesis associated with mutation of energy metabolism genes (complexes I, II, III, IV, V of the mitochondrial respiratory chain) responsible for oxidative phosphorylation, synthesis of ATP and components of the pyruvate dehydrogenase complex [1]. As a result of a violation of energy metabolism, damage to the substance of the brain occurs [1], accompanied by progressive neurological symptoms (muscle hypotension, loss of previously acquired psychomotor skills, seizures in the form of myoclonus, cerebellar and extrapyramidal disorders) [12]. Along with neurological symptoms, cardiomyopathy and liver failure develop [13], lactic acidosis [8], and a specific X-ray picture of degenerative brain changes. The manifestation of the disease occurs at an early age [8], or preschool [4], even less often – in adolescence [2] and can be provoked by intercurrent diseases [1].

The incidence of Ley syndrome is 1 in 36,000 newborns [1]. The type of inheritance is autosomal recessive [6], but may have mitochondrial or X-linked recessive inheritance (depending on the mutant gene responsible for the formation of the mitochondrial complex) [5].

A clinical case. The child (girl) is 4 years old, urgently admitted to the City Ivano-Matrenenskaya Children's Clinical Hospital (GIMDKB) with complaints of convulsive contractions in the extremities, periodic vomiting, weakness, gait disorder (turns her right leg outwards when walking, bends her knee), lower back pain, soreness in the lower extremities.

Anamnesis. A child from the first pregnancy, the first birth. The pregnancy proceeded without any peculiarities. Delivery on time is 39 weeks, independent, the age of the parents at the time of delivery: mother is 24 years old, father is 61 years old. Birth weight 3200 g, body length at birth 51 cm. She grew and developed according to her age. He is registered at a dispensary with a gastroenterologist with a diagnosis of gastroesophageal reflux disease (GERD) of the 3rd degree, a reactive state of the pancreas. All vaccinations are age-appropriate. There were no blood transfusions. It was not possible to identify the hereditary burden.

The disease began acutely 6 months ago with an increase in body temperature to 40 ° C, treatment did not help, the fever lasted for 3 days.

She was taken to the district hospital with a diagnosis of acute respiratory viral infections, neurotoxicosis. On the same day, she felt worse, lost consciousness, and was transferred to the intensive care unit. PCR (polymerase chain reaction) for COVID-19 is positive. I received ceftriaxone and mannitol. Computed to-

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mography (CT) of the brain revealed no focal changes. The condition is without positive dynamics. She was transferred to the regional clinical children's hospital, where she was diagnosed with grade 3 GERD without esophagitis (vomiting syndrome). Metabolic disorders (hypercholesterolemia), cardiac arrhythmia. A nuclear magnetic resonance imaging of the brain was performed, which revealed gliosis of the brain. She was discharged with improvement.

6 months after discharge, her condition deteriorated sharply, which is why she was hospitalized in the HIMDKB.

Objective status. The condition is serious. The temperature is at normal and subfebrile levels. There is no vomiting upon admission. The child is conscious, answers questions late, correctly. Sluggish, hypodynamic. Visual response is preserved, friendly, horizontal nystagmus. Divergent squint, watching objects. You can't stand on your own. There are no seizures. Hyperesthesia. The skin is pale, the turgor is preserved. There is no swelling. There is hyperemia of the arches in the throat, hypertrophy of the palatine tonsils of the 1st degree, the tongue is overlaid with a yellow plaque along the middle line.

The biochemical blood test increased the level of C-reactive protein (CRP) to 6.9 mg/l.

MSCT of the brain with contrast was performed. Conclusion: signs of partial concretion of C2-C3 vertebrae. Otherwise, no pathological changes were detected.

During the examination by an ophthalmologist, the alleged diagnosis was made – pronounced hypoxic changes in the optic disc with its atrophy.

Tandem mass spectrometry (MS/MS) for the quantitative determination of amino acids, succenylacetone, free carnitine, acylcarnitines revealed no significant deviations. Of the studied parameters, only proline 78.8 mmol/l was below the norm (at a norm of 89.8-305 mmol/l).

Based on anamnestic, clinical, laboratory, and instrumental data, the diagnosis was made: unspecified quadriparesis. Nystagmus. Differential diagnosis: encephalic demyelinating process.

Further, during the next 3 months after hospitalization, there was a deterioration in the general condition and an aggravation of the MRI picture of the brain and spinal cord by the type of acute demyelinating encephalomyelitis. Foci of demyelination appeared in the basal nuclei (pale ball on the right, white matter of the legs of the brain, right cerebellar pedicle, hemispheres of the cerebellum, medulla oblongata, spinal cord to the level of C7, which may correspond to the course of acute demyelinating encephalomyelitis). The picture of the epiphysis cyst, moderate expansion of the internal cerebrospinal spaces (Fig. 1, 2, 3).

Immunological changes were noted: the phagocytic activity of leukocytes was reduced, the level of JgG was reduced (0.611 g/l, norm 4.53 – 9.16 g/l; 0.0526 g/l, norm 5.40-18.22 g/l), bilateral polysegmental pneumonia joined. A toxic allergic reaction developed during immunoglobulin treatment. There were signs of systemic inflammatory response syndrome, generalized edematous syndrome, hypoproteinemia, reactive pericholecystitis, pancreatitis.

Moderate respiratory distress syndrome (RDS), pulmonary hypertension, and increasing cardiovascular insufficiency have joined. Pronounced quadriparesis remained in the neurological status. The level of erythrocytes decreased to 2.92×109, the hemoglobin level was 80 g/l. In the biochemical analysis of blood, hypoalbuminemia, hypoproteinemia were noted, a small-point rash appeared on the trunk, limbs, and the temperature rose to 37.7 ° C. DIC syndrome has developed. A hemotransfusion of erythrocyte mass was performed with a positive effect.

However, the condition worsened further, the patient was immersed in a drug-induced sleep, while the signs of severe RDS persisted, effective breathing could be maintained only on 90% oxygen. By this point, the leading pathogenetic syndrome determining the severity of the condition was cerebral, respiratory and cardiovascular insufficiency.

This was followed by a deterioration of the picture on MSCT: damage to the white matter of the brain (mainly the frontal-parietal lobes symmetrically on both sides, with hemorrhagic impregnation in the right frontal lobe, damage to the knee of the corpus callosum). Signs of widespread lesions of the white matter of the frontal, temporal and occipital lobes on both sides, the white matter of the basal nuclei (outer capsule) on both sides, the corpus callosum with the formation of leukomalacia sites in the frontal lobes with negative MSCT dynamics. Signs of partial concretion of C2, C3 vertebrae.

The main diagnosis was formulated as: Demyelinating CNS disease of unspecified etiology. Multiphase disseminated encephalomyelitis, probably postinfectious, severe progressive course. Bilateral pneumonia of mixed etiology, severe respiratory insufficiency of the 3rd degree, disseminated intravascular coagulation syndrome (DIC syndrome), cardiovascular insufficiency, acute pancreatitis. The immunodeficiency condition is unspecified. Toxic-allergic reaction to immunoglobulin. Common urticaria. Dilation of the esophagus. Non-erosive reflux esophagitis. Insufficiency of the cardia. Superficial gastroduodenitis of the antrum of the stomach. GERD of the 4th degree.

3 months after hospitalization, biological death was diagnosed. Resuscitation measures in full were not effective. Death occurred as a result of cardiac arrest against the background of progressive cerebral insufficiency.

Morphological signs of damage to the brain and spinal cord were posthumously recorded: foci of necrosis of the substance of the brain and spinal astrogliosis, numerous perivascular couplings in the substance of the brain, pronounced dystrophic changes in preserved neurocytes, foci of linear discharge and cellular prolapse in the substance of the brain, foci of a decrease in the number of neurons of the molecular and granular layers

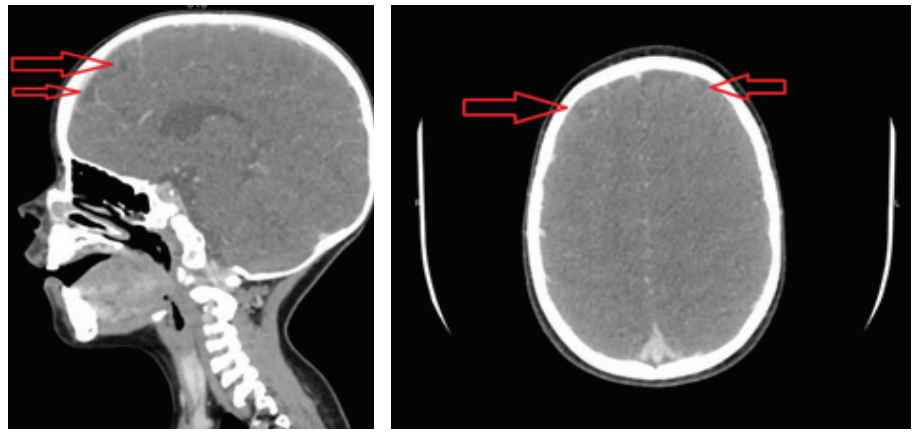

Fig.1. Initial brain changes. 6 months from the beginning of the manifestation of the disease (upon admission to the hospital. The arrows indicate the formation of a cyst

of the cerebellum with focal inclusions of Purkinje cells, fields of gliofibrosis, foci of large-focal encephalomyelolysis, secondary foci of cerebral leukomalacia in the corpus callosum, tissues of the frontal lobe of the right hemisphere, the zone of the central nuclei of the right hemisphere. Postmortem signs of progressive cerebral insufficiency, multiple organ failure syndrome were noted: RDS in the lungs, foci of tubular necrosis in the kidneys, deglycogenesis of the heart, liver, and skeletal muscles. Swelling of the brain and spinal cord. Adrenal adenoma. Morphological signs of secondary immunodeficiency: emptying of follicles of the paratracheal lymph node, as well as lymph nodes of the mesentery and spleen.

Posthumously, full-exome DNA sequencing was performed, which revealed a pathogenic variant of the NDUFS1 gene at position (GRCh37/hg19) chr2:207011681:A>G, position in cDNA c.683T>C with effect p.(Val228Ala). The patient's DNA was analyzed using the Illumina NextSeq550DX genetic analyzer using the pair-terminal reading method (2x151 bp). For sample preparation, the technique of selective capture of DNA sites belonging to the coding regions of human genes (Agilent SureSelect Human All Exon V8 kit) was used, followed by sequencing by synthesis (SBS). The designation of the identified variants was carried out in accordance with the international standards of the HGVS nomenclature (http://varnomen.hgvs.org). Sequencing data processing was carried out using an automated algorithm developed in the Bioinformatics Department of the Federal State Budgetary Budgetary Institution "Medicogenetic Center named afteracademician N.P.Bochkova" (NGS-DATA reg. No. 2021614055, 2021662119, since 2017).

Discussion of the results. Mutations of the NDUFS1 gene cause deficiency of mitochondrial complex I, nuclear type 5. [10]. The mitochondrial complex I (NADH) itself, a multisubunit forming ubiquinone oxidoreductase, is the first enzyme complex in the electron transport chain of mitochondria [10]. It can be fragmented into 3 different fractions: flavoprotein fraction, iron-sulfur protein fraction (IP) and hydrophobic protein fraction (HP). The IP fraction consists of products of *the NDUFS, NDUFS2, NDUFS3, NDUFS4, NDUFS5, NDUFS6* and *NDUFA5* genes [9]. Functionally, this enzyme is considered to be the first protein to accept electrons from NADH-flavoprotein reductase inside the complex [10].

Other researchers [11] have identified the protein encoded by the NDUFS1 gene as a critical substrate of caspase in mitochondria. When mutated, the protein becomes insoluble, but even with such a protein, the cell is able to maintain mitochondrial transmembrane potential and ATP levels during apoptosis. However, there is a decrease in the production of reactive oxygen species in response to apoptotic stimuli. This did not affect the release of cytochrome C and DNA fragmentation during apoptosis, but the morphology of the mitochondria of apopting cells and the integrity of the plasma membrane were preserved [11].

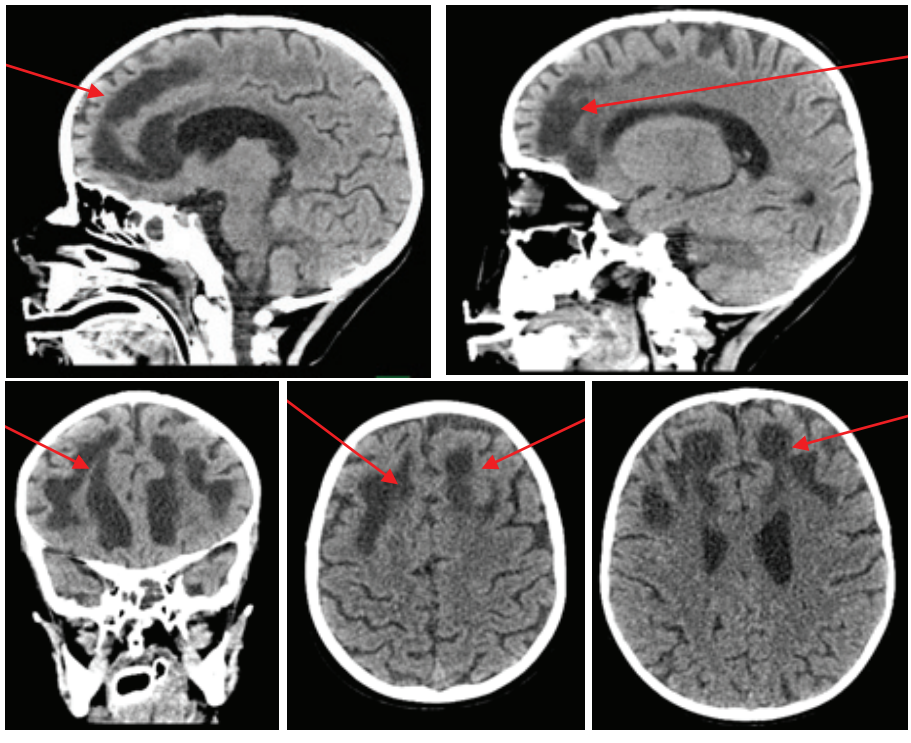

Fig. 2. Brain changes 8 months after the onset of the disease manifestation. Multiple cysts of the brain

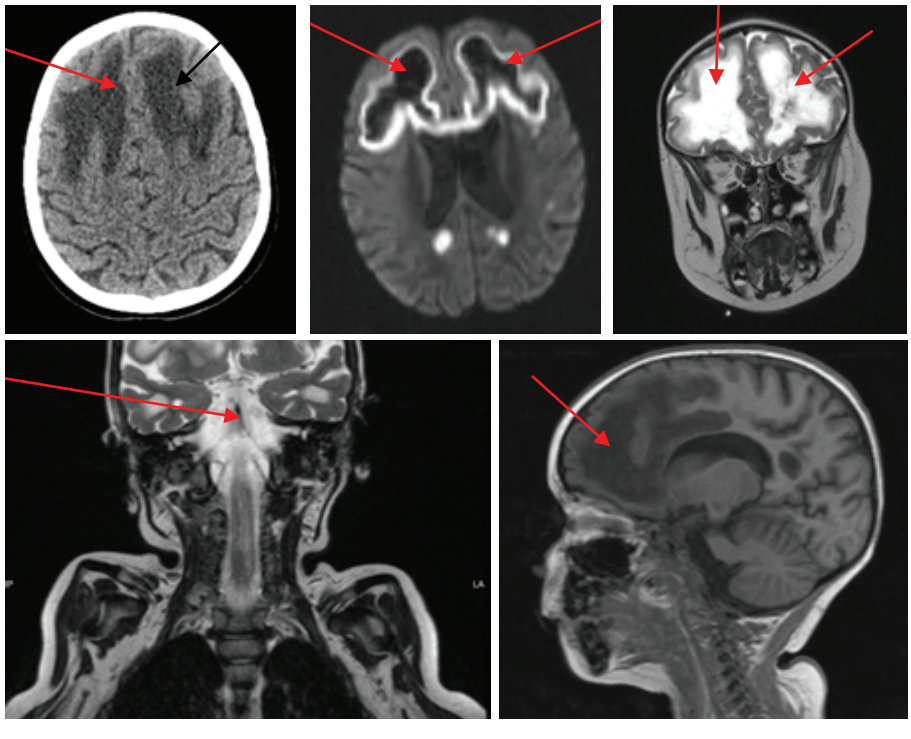

Fig. 3. Brain changes 9 months after the onset of the disease (20 days before the fatal outcome. Multiple cysts of the brain

In general, from the data presented, it can be concluded that the product of the NDUFS1 gene plays an important role in the synthesis of ATP (controlling energy processes), but most importantly regulates the processes of apoptosis (probably triggering autoimmune processes).

Conclusion. At the moment, mitochondrial pathology is difficult to diagnose and has no effective treatment methods. The considered clinical case associated with a deficiency of mitochondrial complex I, nuclear type 5 has severe clinical manifestations and a progressive course. The absence of specific diagnostic markers at the initial stage of development and the rare prevalence of the disease significantly complicates diagnosis. In this regard, it is necessary to pay more attention to the awareness of doctors about hereditary pathology and the role of genetic factors in the structure of general pathology [3].

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

Informed consent to publication. The authors received written consent from the patient's legal representative for the analysis and publication of medical data.

References

1. Lepesova MM, Myrzalieva BD, Kurmanbekova NA, Vaisova EM, & Aitbayeva PR. Podostraya nekrotiziruyushchaya encefalomielopatiya – sindrom Li. Slozhnyj klinicheskij sluchaj [Subacute necrotizing encephalomyelopathy – Ley syndrome. A complex clinical case]. Vestnik Kazahskogo Nacional'nogo medicinskogo universiteta [Bulletin of the Kazakh National Medical University. 2016; 2: 116-118 (In Russ.).]

2. Sukhorukov VS. Ocherki mitohondrial'noj patolgii [Sketches of mitochondrial pastoralism. M.: ID «Medpraxis-M», 2011. P 60-68 (In Russ.).]

3. Tkachuk EA, Seminsky IZh. Rol' genetiki v sovremennoj medicine [The role of genetics in modern medicine]. Bajkal'skij medicinskij zhurnal [Baikal Medical Journal. 2022;1(1):81-88 (In Russ.).] https://doi.org/10.57256/2949-0715-2022-1-81-88 .

4. Haack TB, Haberberger B, Frisch EM, Wieland T, Iuso A, Gorza M, Strecker V, Graf E, Mayr JA, Herberg U, Hennermann JB, Klopstock T, Kuhn KA, Ahting U, Sperl W, Wilichowski E, Hoffmann GF, Tesarova M, Hansikova H, Zeman J, Plecko B, Zeviani M, Wittig I, Strom TM, Schuelke M, Freisinger P, Meitinger T, Prokisch H. Molecular diagnosis in mitochondrial complex I deficiency using exome sequencing. J Med Genet. 2012 Apr;49(4):277-83. doi: 10.1136/jmedgenet-2012-100846. PMID: 22499348.

5. van den Heuvel L, Ruitenbeek W, Smeets R, Gelman-Kohan Z, Elpeleg O, Loeffen J, Trijbels F, Mariman E, de Bruijn D, Smeitink J. Demonstration of a new pathogenic mutation in human complex I deficiency: a 5-bp duplication in the nuclear gene encoding the 18-kD (AQDQ) subunit. Am J Hum Genet. 1998 Feb;62(2):262-8. doi: 10.1086/301716. PMID: 9463323; PMCID: PMC1376892.

6. von Kleist-Retzow JC, Cormier-Daire V, de Lonlay P, Parfait B, Chretien D, Rustin P, Feingold J, Rötig A, Munnich A. A high rate (20%-30%) of parental consanguinity in cytochrome-oxidase deficiency. Am J Hum Genet. 1998 Aug;63(2):428-35. doi: 10.1086/301957. PMID: 9683589; PMCID: PMC1377299.

7. Loeffen JL, Smeitink JA, Trijbels JM, Janssen AJ, Triepels RH, Sengers RC, van den Heuvel LP. Isolated complex I deficiency in children: clinical, biochemical and genetic aspects. Hum Mutat. 2000;15(2):123-34. doi: 10.1002/(SICI)1098-1004(200002)15:2<123::AID-HUMU1>3.0.CO;2-P. PMID: 10649489.

8. Bénit P, Chretien D, Kadhom N, de Lonlay-Debeney P, Cormier-Daire V, Cabral A, Peudenier S, Rustin P, Munnich A, Rötig A. Large-scale deletion and point mutations of the nuclear NDUFV1 and NDUFS1 genes in mitochondrial complex I deficiency. Am J Hum Genet. 2001 Jun;68(6):1344-52. doi: 10.1086/320603. Epub 2001 May 7. PMID: 11349233; PMCID: PMC1226121.

9. Ferreira M, Torraco A, Rizza T, Fattori F, Meschini MC, Castana C, Go NE, Nargang FE, Duarte M, Piemonte F, Dionisi-Vici C, Videira A, Vilarinho L, Santorelli FM, Carrozzo R, Bertini E. Progressive cavitating leukoencephalopathy associated with respiratory chain complex I deficiency and a novel mutation in NDUFS1. Neurogenetics. 2011 Feb;12(1):9-17. doi: 10.1007/s10048-010-0265-2. Epub 2011 Jan 4. PMID: 21203893.

10. DiMauro S, De Vivo DC. Genetic heterogeneity in Leigh syndrome. Ann Neurol. 1996 Jul;40(1):5-7. doi: 10.1002/ana.410400104. PMID: 8687192.

11. Ragan, C. I. Structure of NADH-ubiquinone reductase (complex I). Curr. Top. Bioenerg. 15: 1-36, 1987.

12. Loeffen JL, Triepels RH, van den Heuvel LP, Schuelke M, Buskens CA, Smeets RJ, Trijbels JM, Smeitink JA. cDNA of eight nuclear encoded subunits of NADH:ubiquinone oxidoreductase: human complex I cDNA characterization completed. Biochem Biophys Res Commun. 1998 Dec 18;253(2):415-22. doi: 10.1006/bbrc.1998.9786. PMID: 9878551.

13. Ricci JE, Muñoz-Pinedo C, Fitzgerald P, Bailly-Maitre B, Perkins GA, Yadava N, Scheffler IE, Ellisman MH, Green DR. Disruption of mitochondrial function during apoptosis is mediated by caspase cleavage of the p75 subunit of complex I of the electron transport chain. Cell. 2004 Jun 11;117(6):773-86. doi: 10.1016/j.cell.2004.05.008. PMID: 15186778.