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THE WORLD OF SCIENCE AND INNOVATION

ABSTRACTS OF III INTERNATIONAL SCIENTIFIC AND PRACTICAL CONFERENCE OCTOBER 14-16, 2020

LONDON
2020

THE WORLD OF SCIENCE AND INNOVATION

Abstracts of III International Scientific and Practical Conference

London, United Kingdom

14-16 October 2020

London, United Kingdom

2020

UDC 001.1

The 3rd International scientific and practical conference "The world of science and innovation" (October 14-16, 2020) Cognum Publishing House, London, United Kingdom. 2020. 637 p.

ISBN 978-92-9472-197-6

The recommended citation for this publication is:

Ivanov I. Analysis of the phaunistic composition of Ukraine // The world of science and innovation. Abstracts of the 3rd International scientific and practical conference. Cognum Publishing House. London, United Kingdom. 2020. Pp. 21-27. URL: https://sci-conf.com.ua/iii-mezhdunarodnaya-nauchno-prakticheskaya-konferentsiya-the-world-of-science-and-innovation-14-16-oktyabrya-2020-goda-london-velikobritaniya-arhiv/.

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УДК 616-092.18

MUCOLIPIDOSIS: PATHOGENETIC ASPECTS OF HEREDITARY DISORDERS OF HYDROLASE ACTIVITY

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Abstract: Mucolipidosis Orphan disease, which refers to lysosomal storage diseases. This work considers modern views on the etiopathogenetic aspects of hereditary disorders of hydrolase activity. Provided information about mutations in genes GNTAB and GNPTG; algorithm for biochemical diagnostics. Phenotypically rendered traits in various types of mucolipidosis.

Key words: mucolipidosis, pathogenesis, impaired hydrolase activity, lysosomal diseases, mutations in the GNTAB and GNPTG genes.

Mucolipidosis (ML) - a hereditary autosomal recessive disease associated with decreased hydrolase activity, refers to lysosomal storage diseases. ML today is represented by two types - ML II (I-cell disease) and ML III type (including ML III A/pseudoguller polydystrophy and ML III C). ML type II and III are caused by mutations in the genes GNTAB and GNPTG encoding the enzyme N-acetylglucosamine-1-phosphotransferase (N-AG-1-FT), based on the membranes of the Golgi complex. As a result of insufficiency of N-AG-1-FT there is a violation of accession of mannose-6-phosphate in lysosomal enzymes. Mannose-6-phosphate is the main marker that delivers lysosomal enzymes to lysosomes. In the absence of connection of mannose-6-phosphate with lysosomal enzymes, the latter are not recognized by the cell and do not enter the lysosomes, which leads to their total deficiency. The consequence of this is a violation of intralysosomal degradation of biopolymers - sphingolipids, glycosaminoglycans (GAG), glycoproteins. The activity of lysosomal enzymes is sharply reduced in cultured fibroblasts, and increased in the culture fluid and serum of patients [1, p. 40; 2, 208].

It was found that the GNTAB gene is located on the long arm of chromosome 12 at locus 12q23.3, encodes α- and β-subunits of the enzyme N-AG-1-FT, mutations in the gene responsible for the formation of the clinical picture of ML II and ML III A types. To date, 169 mutations have been described, half of which are missense and nonsense mutations. The GNPTG gene is localized on the short arm of chromosome 16 at locus 16p13.3. Mutations in the GNPTG gene, which selectively encode the γ-subunit of the enzyme N-acetylglucosamine-1-phosphotransferase, lead to the development of ML III C. Clinical symptoms of I-cell disease (ML II) are formed in the presence of a proband deletion of c3503-3504delC , and if the second mutation is represented by a nonsense mutation or a mutation with a shift of the reading frame. The combination of deletion p.3503-3504delTS with missense mutation causes the symptoms of ML III A type [1, p.47; 2, p. 206; 3, p. 206].

Type II ML (I-cell disease) was first described by P. Demars and J. Leroy in 1967. The population frequency is 1: 200,000. The pathogenesis has not been fully studied. It was found that some lysosomal hydrolases, which are excreted by fibroblasts of patients, in culture and electrophoretically differ from the corresponding intracellular enzymes and enzymes that are excreted by normal fibroblasts [5, p. 110]. This invariability, the possibility, access to the excess sialic acid residue present in the molecule of the anomalous enzyme, which leads to the inability of the hydrolase to penetrate into the cells due to adsorption pinocytosis. Insufficiency of N-acetylglucosamine-1-phosphotransferase leads to a decrease in the activity of a number of lysosomal hydrolases, due to the lack of phosphorylation of mannose, which is part of the enzymes. The latter are not "recognized" by lysosomes and are not part of them, because the final mannose phosphate of lysosomal enzymes is a "marker of cognition" for transport proteins [5, p. 111].

The manifestation of the disease begins at birth. Clinical manifestations are similar to the symptoms of MPS type I (Gurler syndrome). Patients lag sharply behind in growth, have pronounced changes in the bones of the skull and skeleton (short neck and chest, congenital hip dislocation, joint contractures, small orbits that lead to moderate exophthalmos). Rough facial features, eyelids with edema, gingival hyperplasia, inguinal, inguinal-umbilical and umbilical hernias, deep mental retardation attract attention. Hepatosplenomegaly and corneal opacity are usually mild. Most patients are diagnosed with heart disease. In infants with ML, the first sign of the disease is often cardiomegaly with the development of congestive heart failure. Sudden death syndrome may be associated with the formation of obstructive hypertrophic cardiomyopathy. For older children, the impression of aortic and mitral valves is characteristic [3, p. 206; 4, p. 210].

For I-cell disease is characterized by a progressive course. Children with this form die in the 2-3rd year of life from complications of the broncho-pulmonary and cardiovascular systems [4, p. 208].

ML III A type (pseudoguller polydystrophy) was first described by V. McKusick et al. In 1965, this type of ML differs from ML type II by a later

manifestation (in the 2nd year of life), less severe course, normal or slight decrease in intelligence (50% of patients), favorable life prognosis (patients live to old age) . The disease is characterized by: short stature, shortening of the torso and upper extremities, stiffness of the joints, scoliosis, thickening of the clavicle, rough facial features, corneal opacity, hernias. Involvement in the pathological process of the cardiovascular system is characterized by damage to the valvular apparatus of the heart with the development of aortic insufficiency, at least - aortic stenosis. ML III type - the mildest form of the disease. The diagnosis of ML is established on the basis of a set of phenotypic traits, the results of biochemical and molecular genetic research methods (mutations in the CNPTAB gene). The first stage of biochemical diagnosis of ML is based on the determination of renal excretion of glycosaminoglycans (GAG). The normal content of GAG in the urine indicates the correctness of the diagnosis of ML, which is assumed and allows to exclude in patients phenotypically similar diseases of accumulation (MPS). The second stage of biochemical diagnosis of ML is to determine the activity of a number of lysosomal enzymes in blood plasma. Among such enzymes, the most informative are β-D-glucuronidase, N-acetyl-alpha-D-glucosaminidase and hexosaminidase (general), the increase in activity of which in 5-15 times serves as an important diagnostic marker of ML. Determination of the activity of lysosomal enzymes - β-glucuronidase, hexosaminidase (total) and N-acetyl-alpha-D-glucosaminidase are performed using chromogenic and fluorogenic substrates. The final stage of diagnosis is molecular genetic research - the search for mutations in the CNPTAB gene. Genomic DNA is isolated from leukocytes of peripheral blood of patients, amplification of all exons of the CNPTAB gene is performed by polymerase chain reaction (PCR) followed by direct non-radioactive sequencing by Senger [1, p. 45; 3, p. 206; 4, p. 210].

Knowledge of the pathogenetic mechanisms associated with impaired activity of lysosamal enzymes, molecular study of GNPTG, CNPTAB genes and identification of mutations allows predicting the severity of ML, contributes to the development of methods of pathogenetic treatment, prevention of disabling disorders, improvement of health status, quality and life expectancy of patients.

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