Modern approach to diagnosis and management of patients with lysosomal acid lipase deficiency

12 December 2015 in Moscow, the first Expert Council was held, it was focused on the modern approach to diagnosis and management of patients with lysosomal acid lipase deficiency.

Lysosomal acid lipase deficiency (LALD) is a rare hereditary disease, that represents accumulation disease with genetic defect of LAL gene and leads to a significant decrease or loss of enzyme activity of lysosomal acid lipase. Such deficiency is characterized by the absence of cholesterol ester breakage and triglycerides in lysosomes and by violation of the functions of internal organs mainly in liver and spleen, and by dyslipidemia.

The importance of multidisciplinary approach to the rare disease was demonstrated by the composition of members of the Expert Council: 17 leading experts of the country in the fields of gastroenterology, hepatology, pediatrics, genetics and neonatology made a speech. The Council was chaired by the Director of the Clinic named after V.H. Vasilenko, Academician V,T, Ivashkin, the Director of the Scientific Research Institute of Pediatrics Corresponding Member of Russian Academy of Sciences L.S. Namazova-Baranova, the Director of FSBSI "Medical Genetics Research Center" Professor S.I. Kutsev.

Russia already has the experience in diagnostics and management of several patients with multiple LALD, some of them get a pathogenic enzyme replacement therapy as a part of clinical research. However, due to low awareness of the medical community about the disease, the diagnosis is often achieved out-of-time, many patients do not receive due attention, which leads to tragic consequences, for instance, the assignment of the child to liver transplantation or to death in infancy during heavy forms of the disease (Wolman disease).

Having exchanged the accumulated experiences of management of patients with LALD, the experts discussed important points in the diagnostics, measures to raise awareness of physicians about this disease were recommended, the decision to develop clinical recommendations on LALD was taken, moreover, it was decided to consider the possibility of including LALD in the "List of life-threatening and chronic progressive rare (orphan) diseases".

The Expert Council work ended in the adoption of a resolution.

The Resolution of the Expert Council summarizing the results of the meeting of December 12, 2015, Moscow "Modern approach to diagnosis and management of patients with a rare hereditary disease - lysosomal acid lipase deficiency"

Objective

Development of a unified approach to the diagnostics and tactics of management of the patients with lysosomal acid lipase deficiency.

Questions for discussion

1. The international terminology and classification of the disease.
2. Modern methods of diagnostics of LALD, screening programs, the differential diagnosis.
3. Possibilities of therapy and tactics of management of the patients.

International terminology and classification of disease

Lysosomal acid lipase deficiency is a rare chronic progressive life-threatening autosomal recessive disorder of lysosomal accumulation caused by mutations in LIPA gene, which result in significant reduction or loss of enzymatic activity of the lysosomal acid lipase (LAL), which leads to chronic accumulation of cholesterol esters and triglycerides in liver, spleen, blood vessel walls and other tissues.

Initially described as separate diseases, Wolman disease (in 1956) and cholesterol esters accumulation disease (in 1963), are now considered as clinical forms of LALD, as they share common etiology and pathogenesis. The age of the onset of the disease and its progression rate are widely variable and may be associated with the origin of the underlying mutation. In the early form of LALD (Wolman disease), rapidly progressive course occurs, with the development of symptoms in the first weeks of life: hepatosplenomegaly, steatorrhea, increased abdominal size, heavy malabsorption syndrome with the development of exhaustion, as well as adrenal calcification. Such patients rarely survive without treatment until the age of more than 6 months. In late form of LALD (cholesteryl ester accumulation disease), there is a combination of dyslipidemia, hepatomegaly, increased transaminase levels and microvesicular steatosis in children and adults. Liver gets damaged in most of the patients, which results in fibrosis, cirrhosis and hepatic failure. If spleen is involved, the signs of hypersplenism and splenomegaly can be observed. Some frequent changes occur, such as the increase in total cholesterol level, triglycerides, low density lipoprotein cholesterol and reducing of lipoprotein cholesterol levels of high density. Since childhood, violations of the cardiovascular system may be manifested, due to early atherosclerosis.

The exact prevalence figure of LALD is unknown and variable due to factors of ethnicity and geographical location, as well as the possibility of diagnostic errors. According to the foreign sources, the prevalence ranges from 1:40 000 to 1:300 000, in Russian the estimated prevalence reaches 1: 100 000. In this connection, LALD is a rare (orphan) disease. Both forms of lysosomal acid lipase deficiency (Wolman disease and cholesteryl ester accumulation disease) are included in the list of rare (orphan) diseases of the RF Ministry of Healthcare (code ICD-10 E75.5).

LALD is caused by mutations of *LIPA* gene, which have been so far discovered in number of more than 40, related to violations of the enzyme function. Since LALD is an autosomal recessive disease, the individuals affected are usually either homozygous or compound heterozygous according to mutations of *LIPA* gene, although in some patients there may be mutations, not detectable by standard methods of DNA analysis. The most serious damage, such as nonsense mutations, gene reconstructions, mutation with frameshift are usually detected in heavy course of the disease — Wolman disease.

Modern methods of diagnostics of LALD, screening program, differential diagnosis

The diagnosis LALD may be suspected in the presence of a combination of changes in the liver (hepatomegaly, increased transaminase activity, signs of steatosis) and lipid profile disorders. Timely diagnosis appears to be complex because of the absence or sparsity of patient complaints, in spite of the progression of liver pathology. In many cases, LALD is an incidental finding, for example, when changes are detected in biochemical analysis of blood or in liver ultrasound study.

LALD diagnosis is confirmed when based on the detection LAL activity deficiency that biochemically measured — by determining the enzyme activity in culture of fibroblasts,

peripheral blood leukocytes. One of the most reliable methods is considered measuring LAL activity in dry blood spots on special diagnostic filters. A blood test for LAL can act as a powerful tool in screening programs and large-scale studies of LALD, it can also be adapted for screening newborns. DNA diagnostics for detection of mutations of *LIPA* gene is an additional method of research. Although most of the affected patients are homozygous or compound heterozygous with respect to *LIPA* gene mutations, some of them may have intronic mutations, not detected during a standard genetic screening.

The differential diagnosis is conducted with liver diseases, disorders of lipid metabolism and other rare accumulation diseases. In patients with hepatomegaly and constantly elevated levels of transaminases in blood serum, incorrect diagnoses may include non-alcoholic fatty liver disease, nonalcoholic steatohepatitis or cryptogenic liver disease, or the case may not be diagnosed at all. To exclude more common diseases such as viral hepatitis and autoimmune liver disease, it is necessary to carry out a full assessment of viral and immunological profile. Based on the lipid profile disorder, incorrect diagnosis of familial hypercholesterolemia, family apolipoprotein B defect and polygenic hypercholesterolemia can be made. Among rare accumulation diseases, differential diagnosis can be carried out with tyrosinemia of type 1, galactosemia, Niemann-Pick disease, Gaucher's disease, Konovalova-Wilson disease, defects in β-oxidation of fatty acids.

The therapy possibilities and patient management tactics

For the moment, the only pathogenetic treatment of lysosomal acid lipase deficiency is an enzyme replacement therapy with sebelipase alfa — recombinant human lysosomal acid lipase, using which demonstrated sufficient effectiveness and relative safety in international clinical researches. Sebelipase alfa drug is registered in Europe and the USA. In Russia, the expected registration of orphan drug is extremely important, because Russian patients are in need of life-saving therapy.

In view of the above, experts consider it necessary to recommend the following measures to improve the quality of medical care for patients with LALD in the Russian Federation, to reduce mortality and disablement, to improve the quality of life of these patients:

1. It is necessary to develop an educational program for doctors on "Rare metabolic disorders in the differential diagnosis of liver diseases" in order to increase awareness among doctors of various specialties and for timely diagnosis of LALD; it is also necessary to include a section on LALD in subjects on liver diseases of physicians programs of continuous medical education.
2. It should be recommended to the main experts in gastroenterology, pediatrics, neonatology, genetics, neurology, cardiology to include determining of the lysosomal acid lipase activity in patients with diseases accompanied by hepatomegaly, hepatosplenomegaly, increased transaminases and lipid spectrum changes, especially in cryptogenic liver conditions, in the standards of diagnosis and medical help. Also, informational letters should be prepared on measures for timely diagnosis of LALD for doctors of all these specialties.
3. Taking into account the potential growth of LALD detection in Russia, a systematic approach to management of these patients is needed. In this purpose, clinical guidelines on providing medical help to patients with LALD should be prepared separately for children and adults. The involvement of professional scientific societies and interdisciplinary approach to preparation of the guidelines would be of particular

value (together with geneticists, pediatricians, hepatologists, neonatologists, neurologists, cardiologists).

4. For the purpose of timely diagnosis of early forms of LALD and reduction of infant mortality because of LALD, and given the availability of the test on the enzyme activity, a program of selective screening in high-risk groups of infants with hepatosplenomegaly, steatorrhea, increased abdominal size, malabsorption syndrome with exhaustion should be developed.
5. The possibility of enzyme replacement therapy with drug sebelipase alfa within the existing programs of early access to the drug should be timely considered in life-saving indications in patients with clinical and laboratory manifestations of LALD in order to reduce mortality and prevent the development of serious.
6. The continuity of the management of patients with LALD from the neonatal, child to adult medical care network should be provided, for this purpose joint activities of children's and adult gastroenterologists, hepatologists, geneticists should be held on a regular basis, including extended counciliums with the discussion of clinical cases.
7. Based on the current data on the severity of the disease and a high risk of developing of irreversible and life-threatening conditions, the inclusion of the disease LALD in the "List of life-threatening and chronic progressive rare (orphan) diseases that lead to reduction in life expectancy of the citizens or their disablement" should be considered during the next review.
8. For providing coordination, methodical and educational activity in the field of diagnostics, differential diagnostics and treatment of LALD, it is suggested to consider the possibility of establishing and regular work of the authorized Expert Council.

Resolution adopted by the members of the Expert Council will be published in magazines, on Web sites on the relevant therapeutic fields and directed to the regional healthcare authorities and specialized experts.

Members of the Expert Council

Chairpeople:

*Ivashkin Vladimir Trofimovich***,** Doctor of Medical Sciences, Professor, Academician of the RAS, Head of the Department of Propaedeutics of Internal Diseases of the Medical Faculty, the Director of the Clinic named after V.H. Vasilenko at the Medical University SBEI HPE "the First I.M. Sechenov MSMU" of the RF Ministry of Healthcare, Head Gastroenterologist of the RF Ministry of Healthcare

Kutsev Sergei Ivanovich, Doctor of Medical Sciences, Professor, Director of FSBSI "Medical Genetics Research Center", Head Specialist in Medical Genetics of the RF Ministry of Healthcare

Namazov-Baranova Leila Seimurovna, Doctor of Medical Sciences, Professor, Deputy of the Director of SCCH in scientific work, Director of the Scientific Research Institute of Pediatrics, corresponding member of the Russian Academy of Sciences

Experts:

Gundobina Olga Stanislavovna, Candidate of Medical Sciences, Doctor of the highest category, Head of the Department of Diagnostics and Rehabilitative Treatment of children with digestive system diseases of the system of the Research Scientific Institute of Preventive

Pediatrics and Rehabilitation Treatment FSAI "Scientific Center of Children Health," of the RF Ministry of Healthcare

Dyagtereva Anna Vladimirovna, Candidate of Medical Sciences, Professor, Head of the Scientific Advisory Pediatric Department FSBI "V.I. Kulakov Scientific Center for Obstetrics, Gynecology and Perinatology" of the RF Ministry of Healthcare, Professor of Neonatology Department of SBEI HPE "the First I.M. Sechenov MSMU" of the RF Ministry of Healthcare

Zharkova Maria Sergeevna, Candidate of Medical Sciences, Doctor of the highest category, Head of the Department of Hepatology Clinic named after V.H. Vasilenko UCH № 2 SBEI HPE "the First I.M. Sechenov MSMU" of the RF Ministry of Healthcare

Zakharova Ekaterina Yurievna, Doctor of Medical Sciences, Professor, Head of the Laboratory of Hereditary Exchange Diseases of FSBSI "Medical Genetics Research Center"

Zakharova Irina Nikolaevna, Doctor of Medical Sciences, Professor, Head of the Department of Pediatrics RMAPE of the RF Ministry of Healthcare, Honored Doctor of the RF, Head Pediatrician of the Central Federal Region of the RF

Zubkov Viktor Vasilievich, Doctor of Medical Sciences, Professor, Head of the Department of Neonatology and Pediatrics FSBI "V.I. Kulakov Scientific Center for Obstetrics, Gynecology and Perinatology" of the RF Ministry of Healthcare

Maevskaya Marina Viktorovna, Doctor of Medical Sciences, Professor, Head Research Scientist of NIE of Innovative Therapy of SEC center of SBEI HPE "the First I.M. Sechenov MSMU" of the RF Ministry of Healthcare, Vice-President of the Russian Society of the Research on the Liver

Mikhailova Svetlana Vitalievna, Doctor of Medical Sciences, Head of the Department of Medical Genetics of the Russian Children's Clinical Hospital

Palgova Lyudmila Konstantinovna, Doctor of Medical Sciences, Professor of the Department of Gastroenterology and Dietetics of SBEI HPE "I.I. Mechnikov NW State Medical University"

Polyakova Svetlana Igorevna, Doctor of Medical Sciences, Professor, Leading Research Scientist of the Scientific Research Institute of Emergency Children's Surgery and Traumatology

Rogozina Natalia Vasilievna, Candidate of Medical Sciences, Doctor of the highest category, an employee of the Department of Viral Hepatitis and Liver Diseases of FSBI "SRI of Children’s Infections" FMBA

Strokova Tatiana Viktorovna, Doctor of Medical Sciences, Professor, Head of Department of Dietetics and Nutrition RNR Medical University named after N.I. Pirogov, Head of the Department of Paediatric Gastroenterology, Hepatology and Dietics of the Clinic of the FSBSI "SRI of Nutrition", Professor of Dietics Department of the RMAPE