OPTIMIZATION OF APPROACHES TO DIAGNOSIS AND TREATMENT OF HYPOPHOSPHATASIA

The Expert Council on optimization of approaches to diagnosis and treatment of hypophosphatasia – a rare hereditary disease accompanied by skeletal and dental alterations, as well as by multiple organ manifestations, which may be fatal – convened in Moscow on April 21, 2015.

The meeting was dedicated to the issues of efficient diagnosis of hypophosphatasia, search for the ways of improving detectability of such patients in Russia and discussion of possible ways of delivery of timely care.

Due to importance of a multidisciplinary approach to the successful solution of the problems at hand the Expert Council involved the leading specialists from different spheres: pediatric endocrinologists, geneticists, laboratory diagnosticians, orthopedists and pediatric nephrologists.

The participants discussed epidemiology of hypophosphatasia, which partially reflects the insufficient level of diagnosis thereof in different countries, analyzed the latest scientific data on the used diagnostic algorithms and new possibilities of pathogenetic therapy and shared experience of managing patients with this pathology.

Expert Council meeting adjourned with a resolution.

EXPERT COUNCIL RESOLUTION

Objective. Improvement of diagnosis and quality of medical care for patients with hypophosphatasia in the Russian Federation, reduction in the rates of mortality and incapacitation, improvement of quality of life of patients with hypophosphatasia. Development of measures of early access to pathogenetic therapy for the patients requiring life-saving treatment.

Definition. Hypophosphatasia is a progressive hereditary metabolic disorder caused by alkaline phosphatase deficiency due to gene *ALPL* mutation, which encodes non-specific tissue isoenzyme of alkaline phosphatase. Insufficient alkaline phosphatase activity results in hypomineralization, skeletal disorders and multisystemic complications.

The disease may set on at any age, even in the intrauterine period. Severity of symptoms of this disorder varies from moderate (benign) to severe (causing incapacitation in adulthood). The disorder is the severest when it sets on in the prenatal period or in the infancy: mortality may reach 90-100% in such cases.

Classification of hypophosphatasia is based on the age of onset of the first symptoms of this disorder. The following forms are classified:

- perinatal (symptoms develop antenatally or at birth);
- infantile (before 6 months of age);
- childhood (6 months – 18 years of age);
- adult (over 18 years of age).

There is also a separate form of hypophosphatasia – odontohypophosphatasia, which is characterized by isolated dental injuries.

Clinical manifestations of hypophosphatasia

Perinatal and infantile forms are characterized by pronounced hypomineralization and rickets-like skeletal deformation, development of pulmonary insufficiency and vitamin B_6-dependent convulsions. Later, low muscle tone, anergic sucking, growth inhibition, insufficient body weight gain, rickets and nephrocalcinosis are observed in such patients.

Childhood hypophosphatasia is characterized by skeletal disorders, low height, fractures, ostealgiae and myalgiae, non-progressive myopathy, joint stiffness, delayed walking, waddling gait and early loss of deciduous teeth.

Adult hypophosphatasia is characterized by numerous poorly healing fractures, which often require surgical interventions. The disease primarily affects lower limbs; shortening and bowing of long tubular bones, impaired gait and low height occur. Chondrocalcinosis, pseudogout and arthropathies accompanied by severe pain and leading to disability are often observed.

Diagnosis. Hypophosphatasia may be suspected in any patient upon detection of low blood level of alkaline phosphatase in the setting of clinical pattern of a rickets-like disease. The key differentiating signs of the disease are low activity of alkaline phosphatase and high blood level of pyridoxal phosphate (active form of vitamin B_6). As the normal level of alkaline phosphatase depends on age and sex, these factors must be considered when interpreting results.

Differential diagnosis. Despite clear prognostic criteria, skeletal disorders at hypophosphatasia resemble other diseases accompanied by rickets and/or osteomalacia, which is why such patients are often diagnosed incorrectly. If hypophosphatemic rickets, vitamin D-deficient rickets, renal bone disease, cleidocranial dysplasia and idiopathic juvenile osteoporosis is suspected, hypophosphatasia must be ruled out to avoid such mistakes.

Treatment. The only pathogenetic therapy of hypophosphatasia is enzyme replacement with asfotase alfa (specific recombinant alkaline phosphatase). Several international clinical trials demonstrated normalization of alkaline phosphatase substrate levels, considerable improvement of locomotive function and positive dynamics of radiographic changes and bone mineralization. Asfotase alfa has not been registered in the Russian Federation yet, which is why Russian patients have only a limited access thereto.

Medical care quality improvement measures. Taking the aforementioned into account, experts deem necessary to recommend the following measures directed at medical care quality improvement, decrease in mortality and incapacitation rates and improvement of quality of life of the patients with hypophosphatasia in the Russian Federation.

1. Development of educational program “Systemic impaired calcium-phosphorus metabolism-related skeletal disorders” for physicians is required to improve awareness of physicians of various profiles and detection of patients with hypophosphatasia.
2. Introduction of obligatory determination of the alkaline phosphatase level in all patients with any diseases involving systemic skeletal disorders (skeletal deformities, growth inhibition, premature loss of teeth) to standards of diagnosis and medical care should be recommended to key specialists in the following spheres: orthopedics, neonatology, endocrinology and pediatrics. In the event of development of a clinical pattern involving generalized convulsions accompanied by respiratory distress and systemic skeletal changes in the neonatal period, alkaline phosphatase level should be assessed.
3. The following assays should be performed in the event of a combination of clinical manifestations of a rickets-like disease and reduction in the alkaline phosphatase level.
• pyridoxal-5-phosphate level;
• gene *ALPL* mutation;
• urine phosphoethanolamine level (if possible).
4. Development of clinical recommendations for laboratory diagnosis of hypophosphatasia involving determination of reference sex- and age-dependent levels of alkaline phosphatase is required to unify interpretation of results of diagnostic alkaline phosphatase activity studies.
5. A possibility of enzyme replacement therapy with asfotase alfa within the existing programs of early access to this drug should be considered to reduce mortality and prevent development of severe complications in the event of life-saving indications in patients with clinical and laboratory manifestations of hypophosphatasia.
6. A possibility of establishment and regular operation of an authorized Expert Council has been proposed to consider in order to ensure coordination, methodological and educational activity in the spheres of diagnosis, differential diagnosis and treatment of hypophosphatasia.

The resolution adopted by the Expert Council participants will be published in specialized magazines, medical web-sites and forwarded to regional healthcare authorities and subject matter specialists.

Chairmen: Sergey Ivanovich Kutsev, Valentina Alexandrovna Peterkova.

Experts: N.A. Belova, N.S. Demikova, E.Y. Zakharova, N.Y. Kalinchenko, A.G. Kochetov, P.V. Novikov, E.E. Petryaykina, N.L. Pechatnikova, S.S. Rodiyonova, S.O. Ryabykh, V.S. Sukhorukov, A.N. Tyulpakov, A.N. Tsygin.