An Expert Council meeting involving international participants headed by chief specialist on medical genetics of the Ministry of Health of the Russian Federation (RF) Professor S.I. Kutsev and chief specialist on medical genetics of the Ministry of Health of the RF and correspondent member of the Russian Academy of Sciences (RAS) Professor V.A. Peterkova and dedicated to definition of the main principles of managing patients and optimizing approaches to treatment of hypophosphatasia (HP) – a rare hereditary disease – took place in Moscow on November 21, 2015.

The Expert Council involved geneticists, pediatric endocrinologists, orthopedists, pediatric nephrologists and other specialists.

An international expert presented experience of treating and tactics of managing patients at the leading world clinics; Russian specialists shared experience of treating such patients in Russia, as well as discussed possible ways of rendering timely care thereto.

Having discussed current understanding of HP (a rare hereditary disease), shared Russian and international experience of treating patients, the Expert Council participants formulated the main principles of managing HP patients. The Expert Council meeting concluded with adoption of a resolution.

Expert Council Resolution

on the definition of tactics of managing patients with hypophosphatasia
following the meeting of November 21, 2015
Moscow

Objective. Definition of the primary principles of tactics of managing patients with HP concerning:

1. prescription criteria of enzyme-replacement therapy for HP patients;
2. monitoring of the treated patients, appraisal criteria of a patient's condition dynamics;
3. monitoring criteria for the patients not subject to pathogenetic treatment.

Definition. HP is a rare, severe, progressive and sometimes a potentially fatal hereditary metabolic disease caused by alkaline phosphatase (AP) deficiency due to mutation of gene *ALPL*, which encodes the tissue-nonspecific isoenzyme of AP. AP activity deficiency results in phosphate and calcium metabolic disorders, bone hypomineralization, skeletal disorders (bone deformation and destruction) and multiple organ complications. Other clinical signs may be as follows: pain syndrome, manifested myasthenia, respiratory failure, convulsions, renal malfunction and motor malfunction, as well as tooth loss. Disease may set on at any age, even intrauterine. Degree of symptom manifestation may vary from moderate to severe (causing incapacitation in adulthood). The disease is the severest when it sets on in fetuses (perinatal form) and infants (infantile form) under 6 months of age. In such cases, mortality may reach 90-100%.

HP may be suspected in any patient with low AP activity (considering age/sex norms) and clinical pattern of the disease. High level of AP substrates, particularly of pyridoxal 5-phosphate (active form of vitamin B_6) may be used to confirm diagnosis. According to the current approaches, genetic analysis is an important diagnostic criterion desirable for establishing diagnosis.

Currently, the only means of pathogenetic treatment of HP is enzyme-replacement therapy (ERT) with asfotase α – specific recombinant AP, the effectiveness and relative safety whereof was demonstrated by multiple clinical trials. Improvement of metabolic parameters (level of alkaline phosphatase substrates), considerable improvement of the radiographic pattern, as well as of bone mineralization, rate of growth and locomotor function were observed in HP patients. Asfotase α is registered in many countries: Europe, USA, Canada and Japan. Registration of this

orphan drug in Russia is an extremely important anticipated event, as Russian patients badly need access to life-saving therapies.

Considering the population size of the RF, as well as the expected spread of severe forms of HP (1:150,000), ca. 1,000 people may require treatment. Currently, Russian patients have only limited access to ERT: participation in clinical trials (under-6 children with infantile form of the disease) and individual-based access to the treatment of life-threatening conditions. The first positive experience of treating patients with HP in Russia has already been obtained, which is why there is a need in uniform monitoring criteria of a patient's condition.

Initiation criteria of a therapy aimed at HP patient mortality and incapacitation rate reduction, as well as improvement of quality of life of such patients, require development and systematization due to versatility of clinical symptoms of HP, degree of manifestation thereof and different age of manifestation of symptoms.

Taking the aforementioned into consideration, expert deem necessary to recommend the following principles of tactics of managing HP patients.

1. Criteria of ERT initiation (including, but not limited to) are as follows:

• Immediate ERT is required by:

▪ children with perinatal or infantile form of HP;

▪ under-3 children with clinical signs of HP.

• Acute ERT is required by:

▪ children with skeletal system disorders (in presence of 1 or more symptoms) – skeletal maldevelopment, rickets-like changes, recurrent fractures (more than 1), atypical fractures (inconsistent with severity of the trauma, indolent fractures; more than 2 fractures);

▪ children with systemic HP-caused disorders (in presence of 1 or more symptoms) – physical developmental delay, delay of motor function development, motor disturbances (including waddling gait), uncontrolled chronic pain syndrome, kidney damage, use of special auxiliary devices for locomotion/fixation etc.;

▪ children with other HP-associated symptoms causing persistent disorders of body functions.

• Non-emergency ERT is required by:

▪ children with skeletal system disorders (in presence of 1 or more symptoms) – atypical fractures (inconsistent with severity of the trauma, indolent fractures; more than 1 fracture), bone alterations caused by impaired mineralization thereof (according to radiography and/or densitometry; osteomalacia, osteopenia, osteoporosis etc.);

▪ children with systemic HP-caused disorders (in presence of 1 or more symptoms) – myasthenia, partially or fully controlled pain syndrome, hypercalcemia, hypercalciuria, premature tooth loss, joint disease;

▪ children with other HP-associated symptoms, which may potentially cause persistent disorders of body functions;

▪ adults with HP symptoms causing persistent disorders of body functions.

• Monitoring (no ERT at the moment) is required by:

▪ over-3 children without subjective or objective HP-caused clinical alterations by the time of a complete examination;

▪ adults without subjective or objective HP-caused clinical alterations by the time of a complete examination;

▪ patients with HP odontoform without signs of persistent body malfunctions.

2. Monitoring of the treated patients should be recommended if the following appraisal criteria of a patient's condition dynamics (including, but not limited to) are met:

• Complaints and complaint trending by means of visual analog scales.

• Anthropometric data (measurement of body length and weight, wrist, head and chest circumference [for children]).

• Respiratory function assessed by means of analyzing respiratory support status (in children with respiratory failure).

• Primary parameters of the cardiovascular function.

• Intracranial pressure parameters.
• Condition of the musculoskeletal system, including joints.
• Muscle strength.
• Gross and fine motor skills, cognitive development assessed by means of developmental scales (for children).
• Plasma pyridoxal phosphate level.
• Blood and urine calcium concentration; $25(OH)_2D$ in blood serum.
• Ectopic calcification foci.
• Radiographic scans with the radiographic global impression of change (RGI-C) scale and the rickets severity scoring (RSS) scale.
• Densitometry parameters (in over-5 children and adults).
• Oral organ checkup (teeth [in order to assess falling out of teeth / teething] and parodontium tissues).
• Adverse events.
• Focal reactions in drug injection sites.
• Parameters of quality of life assessed by means of age-adequate questionnaires.

The recommended monitoring of the treated patients is as follows: at least once per 3 months in under-3 children and at least once per 6 months in over-3 children and adults (at least once per 3 months in the first six months of therapy).
Temporary ERT withdrawal is possible in the event of severe adverse events conclusively associated with the drug. In children, ERT should not be permanently withdrawn until at least 18 years of age. In adults, it is recommended to address the issue of dose reduction or treatment withdrawal when the age/sex-adequate functional condition of the body has been achieved. Rigorous monitoring is required, especially within the first year after dose reduction or drug withdrawal. It is necessary to resolve the issue of therapy mode reestablishment if the condition becomes worse or if HP-associated symptoms, which may potentially cause persistent body malfunctions, are identified.

3. Criteria of monitoring the patients not subject to treatment – identical to the criteria for the treated patients (including, but not limited to).

The recommended monitoring of the treated patients is as follows: at least once per 6-12 months in children and at least once per year in adults. It is recommended to resolve the issue of ERT initiation if the condition becomes worse or if HP-associated symptoms, which may potentially cause persistent body malfunctions, are identified.

4. It is necessary to develop methodological recommendations on tactics of managing HP patients with detailed description of study and patient condition assessment methods.
5. Given significance of the issue of timely diagnosis and treatment of HP in fetuses, neonates and infants and high mortality rate of such patients, it is recommended to actively conduct scientific and educational events for physicians, consider the possibility of an Expert Council on diagnosis of early forms of HP and specify possible approaches to the issue.

The resolution adopted by Expert Council participants is to be published in magazines and web-sites in corresponding therapeutic areas and directed to regional healthcare authorities and subject matter specialists.

Chairmen:

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Director of Federal State Budgetary Research Institution “Medical genetics research center”

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