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PHEX GENE MUTATION IN A CHILD WITH X-LINKED HYPOPHOSPHATEMIC RICKETS

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Introduction. *X-linked hypophosphatemic rickets is part of an extensive group of hereditary diseases characterized by loss of phosphate by the kidneys, which leads to growth disorders, rickets and osteomalacia. These conditions are characterized by a violation of the phosphate balance, which is necessary for the formation of bones.*

Clinical case. *Patient M., at the age of 5, complained of deformity of the bones of the lower extremities, stunting, protruding joints and loss of teeth. Initially, the patient was prescribed calcium orally and orthopedic products for the lower extremities, but the clinical result was unfavorable. Sequencing of the PHEX gene revealed the pathogenic variant c871C>T (p.Arg291).*

Discussion. *X-linked hypophosphatemic rickets is caused by mutations in the PHEX gene; to date, more than 200 mutations have been associated with this disease. Clinically, this disease is characterized by curvature of the lower extremities, decreased growth, complaints of deformities of the musculoskeletal system, dental abscess and other clinical signs and symptoms of rickets.*

Keywords: *X-linked hypophosphatemic rickets, PHEX gene, rickets.*

Topicality. X-linked hypophosphatemic rickets, also known as vitamin D-resistant rickets, familial hypophosphatemic rickets, or phosphate diabetes, is part of a broader group of inherited diseases characterized by loss of phosphate by the kidneys, causing growth disorders, rickets, and osteomalacia (1). These conditions are characterized by a violation of the phosphate balance, which is necessary for bone formation. For example, in X-linked hypophosphatemic rickets, autosomal dominant hypophosphatemic rickets, tumor-induced osteomalacia, hyperphosphatemic familial tumor calcification, oncogenic osteomalacia and hereditary hypophosphatemic rickets with hypercalciuria are included in a group of conditions known as hypophosphatemic syndrome [2,3]. It is estimated that X-linked hypophosphatemic rickets occurs in one out of every 20,000 newborns and has a dominant X-linked heredity. X-linked hypophosphatemic rickets is caused by mutations in the PHEX gene; To date, more than 200 mutations associated with this disease have been described in the literature. These mutations inactivate the PHEX enzyme, making it unable to break down other proteins. The gene is located in Xp22 [5,6]. Clinically, the disease is characterized by curvature of the lower extremities, a decrease in growth rates after the child begins to walk, complaints of the musculoskeletal system, stress fractures, dental abscesses and clinical signs characteristic of rickets [7].

The PHEX gene contains instructions for the production of an enzyme that is active mainly in bones and teeth. It breaks down other proteins into smaller parts; however, proteins cleaved by the PHEX enzyme have not been identified. The PHEX enzyme may be involved in regulating the balance of phosphates in the body. Among the many functions it performs, phosphate plays an important role in bone formation and growth in childhood and helps maintain bone strength in adults. Phosphate levels are largely controlled by the kidneys. The kidneys usually secrete excess phosphate in the urine, and they reabsorb this mineral into the bloodstream when more is needed [7].

The PHEX enzyme may be involved in the regulation of fibroblast growth factor protein 23 (which is produced from the FGF23 gene). This protein normally inhibits the ability of the kidneys

to reabsorb phosphate into the bloodstream. Although it is believed that the PHEX enzyme has some effect on the activity of fibroblast growth factor 23, a direct relationship between them has not been established. It is also unclear how the PHEX enzyme helps control phosphate reabsorption and what role it plays in bone formation and growth [5, 7].

Researchers are not sure how mutations in the PTEN gene lead to low blood phosphate levels (hypophosphatemia) and related bone growth problems in people with X-linked hypophosphatemic rickets. Since many patients have elevated levels of fibroblast growth factor 23, it is likely that mutations in the PHEX gene somehow affect the production of this protein. An increase in the level of fibroblast growth factor 23 reduces the reabsorption of phosphates by the kidneys, which leads to hypophosphatemia. However, since the level of fibroblast growth factor 23 is normal in some sick people, researchers are also considering other ways in which a mutation of the PHEX gene can lead to X-linked hypophosphatemic rickets [8,9].

We report the case of a child with a clinical, radiological and molecular diagnosis of X-linked hypophosphatemic rickets.

Clinical case. A 5-year-old boy turned with symptoms that manifested during the first year of life. The symptoms consisted of deformity of the bones of the lower extremities in combination with protruding joints and loss of teeth, stunting. He received treatment using calcium and lower limb orthoses, but the symptoms did not improve. His mother has a history of deformities of the lower extremities, but no genetic or metabolic studies have been conducted. Other family members did not report bone deformities, growth changes, or genetic studies.

The boy's tests showed the following: increased alkaline phosphatase level – 856 mcg/l (maximum control value 269 mcg/l), normal serum calcium level – 8.9 mg/dl (control range 8.4-10.2 mg/dl) and reduced serum phosphorus level - 1.7 mg/dl (control range 2.9-5.1 mg/dl). In addition, reduced levels of 25-OH-vitamin D were found: 8.77 ng/ml (control range: 30-70 ng/ml) and slightly elevated levels of parathyroid hormone (PTH) - 67.24 pg/ml (control range: 12-65 pg/ml). Renal function (creatinine 0.3 mg/dl), other electrolytes (sodium 138 mg/dl, potassium 4.4 mg/dl and chloride 114 mg/dl) and ultrasound examination of the kidneys were within normal limits. The urine test did not reveal proteinuria or hematuria, and the level of calcium in the urine was normal for 24 hours. The phosphorus/creatinine ratio in urine exceeded 1 (control range 0.05–0.25), and the maximum tubular excretion of phosphate relative to the glomerular filtration rate was 2.3 mg/dl (normal range 2.5–4.5 mg/dl).

An X-ray of the long bones showed dilation of the proximal metaphyses of the femurs and poor clarity of bone contours. Deformities were observed during flexion of the distal diaphyses, similar results were obtained in the radial, ulnar and tibial bones, as well as deterioration of the spine. All results were comparable to metabolic disorders such as rickets or osteomalacia. Radiological changes in the bone tissue were typical in our case. Specific radiological changes in the bones of the extremities were expressed in the distal metaphysis of the radius and ulna: the metaphysis is expanded and deepened (acquires a concave shape), the boundary between the epiphysis and the metaphysis is fuzzy (has the shape of a brush).

Clinical and laboratory parameters raised suspicion of X-linked hypophosphatemic rickets, therefore, genome sequencing was performed. The method of complete exome sequencing (WES) was performed. Approximately 214,000 exons from all encoded sequences were enriched to achieve consensus using fragments of genomic DNA containing more than 340,000 probes for the human genome. Sequencing was performed on the Illumina HiSeq 4000. The sequencing result showed the presence of nonsense homozygous mutation c871C>T (p.Arg291) in the HEXA gene.

After the sequencing results, the diagnosis was established: X-linked hypophosphatemic rickets. X-linked dominant inheritance.

After the diagnosis of the disease, treatment with calcium, calcitriol and phosphorus replacement was initiated. To compensate for the level of phosphorus in the blood, the drug Phospha 250™ Neutral was used, the drug contains potassium phosphate and sodium phosphate.

To correct the deformity of the patient's lower extremities, a corrective splint was used for a long time at night.

During the 7-year follow-up, there was a significant improvement in the deformity of the lower extremities and the growth of the child. Hypophosphatemia, calcitriol intake and phosphorus recovery continues.

Discussion. The PHEX gene has been implicated in the development of X-linked hypophosphatemic rickets, and more than 200 mutations associated with this disease have been reported in the literature [1]. The PHEX gene encodes a metalloprotease belonging to the family of zinc-dependent proteases of type II of the M13 cell membrane and is expressed in bones, teeth, lungs, ovaries, testes and parathyroid gland [5]. It has been reported that the PHEX gene participates in the regulation of fibroblast growth factor-23 (FGF-23) by splitting it into inactive fragments. Inactivation of the PHEX gene prevents the normal degradation of FGF-23, which leads to a decrease in phosphorus reabsorption by the kidneys by suppressing the expression of sodium–phosphorus co-transporters IIA and IIC on the apical surface of the proximal tubule of the nephron, causing an increase in phosphorus excretion in urine. phosphorus. FGF-23 also inhibits the action of 1-α-hydroxylase, which reduces 1α, 25 (OH) 2D3, as well as phosphate absorption in the intestine and bones [2,3,4,5,6,7].

The most common clinical manifestations are changes in height leading to stunting, usually associated with bone deformity and curvature of the lower extremities, as well as symptoms of vitamin D resistance. Bone pain, enthesopathy and rare mild muscle complaints have also been described as part of the clinical spectrum. As growth continues, deformities appear in the lower extremities, such as valgus deformity or varus deformity, secondary to the lesion, in the epiphyseal regions of the distal femur and proximal tibia. Other findings include the chest; dental defects such as abscesses without caries; clinical signs characteristic of rickets such as rickety rosaries, cranial bones, Harrison's groove (a horizontal channel in the lower part of the chest formed by a diaphragm that pushes the ribs inward when they attach); and in adults - development of osteomalacia [7,8,9,10].

Patients have hypophosphatemia, increased alkaline phosphatase levels and normal serum calcium levels, while parathyroid hormone levels may be normal or elevated. Molecular analysis is used to confirm the diagnosis of hypophosphatemic rickets, especially with high FGF-23 levels [8].

Treatment is based on the use of phosphate supplements in the form of salts and metabolites for oral administration, calcitriol or 1-hydroxylated analogues of vitamin D.

Conclusions. X-linked hypophosphatemic rickets leads to impaired bone metabolism in most patients. Early detection and interdisciplinary diagnostic studies are vital for the organization of appropriate treatment and improvement of the quality of life of patients.

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