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A CLINICAL CASE OF OSTEOGENESIS IMPERFECT TYPE III, DETERMINED BY COL1A1 (P.GLY845ARG) GENE MUTATION IN A NEWBORN GIRL

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Summary

Osteogenesis imperfecta (OI) is a disease that is characterized by hereditary connective tissue dysplasia and is clinically manifested as excessive bone fragility and limb deformity. The overall incidence of OI is 1:10,000-20,000 live births. The main autosomal dominant inheritance path, autosomal recessive and X-linked forms have been established, and sporadic cases of the disease, denovo mutations and familial mosaicism have been described. 85% of cases are connected with mutations in the COL1A1 and COL1A2 genes, which leads to quantitative and qualitative changes in the synthesis of type I collagen. Quantitative defects are due to the formation of a null allele, in which the structure of collagen remains unchanging, and its amount is halved. Out of qualitative defects, the most common type of mutation is associated with the replacement of glycine with a larger amino acid. This leads to a disruption in the formation of the triple chain and structural changes in the type I procollagen molecule.

The article presents a clinical case of type III osteogenesis imperfecta caused by a mutation in the COL1a1 (p.Gly845Arg) gene in a newborn girl. Antenatally diagnosed with oligohydramnios and shortening of the limbs, after birth phenotypically revealed congenital dwarfism with short limbs, small size of the cartilaginous skull, hypertelorism, depressed nose bridge and micrognathia. X-ray examination revealed fractures of the humerus. The results of the molecular genetic study revealed the c.2533G>A (p.Gly845Arg) mutation of the COL1A1 gene.

Molecular genetic examination of family members (mother, father and two sisters of the proband) did not reveal the pathological allele diagnosed in the proband, that is, the birth of a child with a hereditary pathology of the musculoskeletal system occurred as a result of a new mutation.

Key words: *Osteogenesis Imperfecta; Mutation of the COL1a1 gene (p.Gly845Arg); de novo Mutation.*

Introduction

Osteogenesis imperfecta (OI) is a disease characterized by hereditary connective tissue dysplasia and clinically manifested as excessive bone fragility and limb deformity. The overall frequency of OI is 1:10 000-20 000 live births, the frequency of type I is 1:30 000, the frequency of type II is 1:60 000, the total frequency of three congenital forms (types II, III, IV) is 1:20 000. However, with a mild course, the disease often remains undiagnosed due to the weak severity of clinical manifestations. The age of manifestation depends on the severity of the course, in severe cases it manifests in utero [1, 2, 7, 8, 9, 12].

According to the literature, the synthesis and maturation of collagen begins in the cell nucleus and ends in the extracellular matrix. Type I collagen is a heterotrimer consisting of two pro-α1(I)- and one pro-α2(I)-polypeptide chains. After translation, pro-α1- and pro-α2-chains are transferred to the endoplasmic reticulum, where the process of formation of the type I procollagen triple helix is initiated. The coiling process requires the presence of post-translational proteins (CRTAP, CyPB, P3H1). The presence of a mutation in the CRTAP, LEPRE1, PPIB genes encoding these proteins leads to the development of the disease. Type I collagen is formed after transport of type I procollagen to the Golgi complex and subsequent exocytosis into the extracellular matrix, cleavage of C- and N-propeptides. The presence of covalent bonds between type I collagens promotes the formation of multiple collagen fibrils, which form collagen fibers, the most important protein in the organic part of the bone tissue [4, 7].

At present, the main autosomal dominant inheritance, autosomal recessive and X-linked forms have been established, and sporadic cases of the disease, denovo mutations, and familial mosaicism have been described. In 85% of cases, mutations occur in the COL1A1 and COL1A2 genes, which leads to quantitative and qualitative changes in the synthesis of type I collagen. Quantitative defects are due to the formation of a null allele, in which the structure of collagen remains unchanging, and its amount is halved; the course of the disease in this case is mild. Out of the qualitative defects, the most common type of mutation is associated with the replacement of glycine with a larger amino acid in one of the α-chains that make up the collagen triple helix, which leads to a disruption in the formation of the triple chain and structural changes in the type I procollagen molecule [1, 2, 7, 9].

In other cases, the disease develops as a result of a mutation in the genes of proteins involved in post-translational modification, chaperone attachment,

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collagen folding and cross-linking. In patients with OI, changes in the process of bone tissue formation were also revealed, which were not associated with collagen, but with a violation of bone mineralization, differentiation and functioning of osteoblasts. This improved understanding of the cellular and biological pathogenesis of OI [7].

As a result of the biosynthesis of defective collagen in patients with OI, the formation of the bone matrix is disturbed, while the balance between resorption and bone formation changes towards the predominance of resorption. A child with growing OI has thin bone with impaired trabecular structure, a thin cortical layer, and a high level of remodeling, which leads to an extremely high risk of fractures. As a result of mutations, the altered α-chain undergoes the folding process more slowly, and therefore the enzymes that carry out post-translational modification interact with the α-chain for a longer time and disrupt its structure. These changes lead to disruption of exocytosis and cross-linking of collagen molecules into fibrils, which can lead to the activation of the apoptosis mechanism. As a result of these changes, the architectonics of bone tissue is disturbed. The mildest and most common forms of OI are due to premature codon termination or a defect in RNA splicing, which leads to disruption of type I collagen biosynthesis by osteoblasts. In patients with severe forms, the processes of bone remodeling are accelerated [4, 7].

To date, 20 genes are known, which mutations cause OI. Violations of post-translational modification of collagen, a defect in hydroxylation are caused by the genes CRAPT, LEPRE1, PPIB; violation of bone tissue formation and mineralization – IFITM5, SERPINF1; terminal propeptide cleavage defect – BMP1; impaired interaction with chaperones and cross-linking of collagen – SERPINH1, FKBP10, PLOD2; impaired differentiation and functioning of osteoblasts – SP7, TMEM38B, WNT1, CREB3L1, SPARC, MBNPS2 [1, 4, 9].

The first classification was proposed by D.O. Sillence (1978), supplemented by M. Ramachandran and based on the data of clinical and radiographic examination of the patient, distinguishes 4 main types of the disease with predominantly AD-type of inheritance. At the moment, the classification of D.A. Sillence is more commonly used in clinical practice. In 2009, the unique classification was supplemented by F.N. Glorieux with four other types of OI (V – with AD-type and VI, VII, VIII – with AR-type of inheritance, which are not associated with type I collagen pathology). However, the use of this classification in routine clinical practice is difficult due to the lack of clear differences between the new types and the classic four types [1, 7, 11].

In 2009, at the meeting of the International Committee for the Nomenclature of Constitutional Skeletal Disorders (INCDS), the distribution of OI types into 5 groups was proposed: 1. Violations of the synthesis and structure of collagen; 2. Violation of bone mineralization; 3. Violation of post-translational modification of collagen; 4. Violation of collagen maturation and chaperone attachment; 5. Violation of differentiation and maturation of osteoblasts.

All mutations that will increase the genetic heterogeneity of the disease in the future will be distributed as subtypes of phenotypic groups. To complete this classification, a large group of syndromes was added, which were also accompanied by reduced bone mineral density and had a cross-clinical picture with OI. Characterization of phenotypes according to the new classification is described in F.S. VanDijk and D.O. Sillence. The full version of the classification was published in Nosology and Classification of Genetic Skeletal Disorders in 2015 [5]. Significant genetic and phenotypic polymorphism of OI, the lack of genotypic-phenotypic correlation, similarity of clinical manifestations, complexity of diagnosis indicate the need for new generation sequencing technologies.

OI type I is the mildest and most common form of the disease. Patients produce collagen of normal quality, but in small quantities. Fractures occur postnatally, and the incidence of fractures decreases or even stops after puberty. The risk of fractures in OI type I increases in women after menopause and in men after 60. Patients with type I OI have blue sclera, an increased tendency to hemorrhage, hearing loss or hypermobility syndrome, slight growth retardation, and slight deformities of the long bones. Based on the presence or absence of dentinogenesis imperfecta, OI subtypes A and B are distinguished [1].

OI type II is the most severe form of the disease, accompanied by a high rate of perinatal mortality. In most cases, children die within the first year of life due to respiratory failure or intracranial hemorrhage. Such children are often born with a delay in fetal development and physiological gestational age. Over time, severe deformities of the extremities are formed, on radiographs, long tubular bones have pronounced osteoporosis, signs of intrauterine fractures and abnormal modeling. The growth of children with OI type II is low. Skull with pronounced delayed mineralization and wide fontanelles. Sclera is grey-blue. Bones consist mainly of bone tissue without haversian canals or with a disordered arrangement of plates. Collagen is of insufficient quantity or quality [1, 10].

Type III OI is known as the progressive deforming variant. Dentinogenesis is imperfect. There may be breathing problems and early hair loss. Most patients with OI type III have a severe form of bone dysplasia in childhood. They have extremely fragile bones, they register up to hundreds of fractures throughout their lives. Long tubular bones are easily deformed from normal muscle tension and due to fractures, have a pronounced growth retardation, almost all patients develop scoliosis. X-ray – wide metaphyses, layering like "popcorn" in the growth zones in addition to osteoporosis. Collagen is of insufficient quality [1].

OI type IV is a very severe form. Diagnosis can be made at birth or at school age. Features of the phenotype: the color of the sclera can be different, early hair loss, imperfect dentin genesis. These children often have several fractures per year and a curvature of the long bones. The frequency of fractures may decrease both may not even be after puberty. In general, patients with type IV OI have a low final height. Many of these patients respond to growth hormone therapy and may grow

significantly. Bone X-rays show osteoporosis and mild modeling abnormalities. Many patients have vertebral compression fractures and scoliosis. With constant rehabilitation and orthopedic correction, these patients can move without assistance. Collagen is of low quality [1].

Osteogenesis imperfecta types II and III can be diagnosed prenatally by ultrasonography, since fetuses with this pathology usually have intrauterine fractures. The disease is confirmed by antenatal laboratory studies: chorionic villus biopsy with cultivation of cells demonstrating the production of abnormal type I collagen in the form of post-translational super modification of procollagen on electrophoresis; chorionic villus biopsy/ amniocentesis to obtain fetal DNA for molecular analysis of genes involved in the development of OI. Pre-implantation or prenatal genetic diagnosis is possible in cases where pathological variants of gene mutations are already known in the family. The purpose of such an examination is to exclude the implantation of an embryo carrying a pathogenic mutation or termination of pregnancy [1].

Postnatal diagnosis of OI is based on data obtained from the collection of anamnestic reports, clinical manifestations and results of radiography (osteopenia, osteoporosis, fractures, deformities of long tubular bones, additional skull bones), osteodensitometry (assessment of tooth tissue and bone density), laboratory diagnostic data (determination of serum concentrations of vitamin D, calcium, phosphorus, parathyroid hormone and alkaline phosphatase) and specific biochemical parameters of bone metabolism. At the initial diagnostic search, it is important to exclude metabolic causes of osteoporosis and fractures [3, 7, 11].

To facilitate diagnosis, the most characteristic features of OI have been deduced: hereditary history or recurrent fractures; idiopathic fractures and/or bones calluses; short stature; blue sclera; imperfect dentinogenesis; progressive hearing loss; ligament weakness; "fish" vertebrae, as a result of compression fractures of the spine (mainly in adult patients); wormian (additional) bones in the region of the sutures of the skull (up to 4-6 mm) in diameter; acetabular protrusions; low bone density (radiological, densitometry). The key diagnostic point of OI is the generalization of the nature of connective tissue defects, which can be in various combinations, in particular, facial defects (triangular or flattened skull, blue sclera, opal teeth), macrocephaly, chest deformity (barrel-shaped or funnel-shaped), hypermobility joints, morphological changes in the vertebrae, growth retardation [1, 8, 11].

The International Osteoporosis Foundation recommends the use of reference markers of bone metabolism in all clinical studies, namely markers of bone resorption (type I collagen C-terminal telopeptide, CPT) and bone formation (type I pro-collagen N-propeptide, P1NP).

Genetic research is used to diagnose mild forms of OI and in the absence of characteristic phenotypic traits. Determining the type of OI is important for assessing the severity of the disease, predicting complications of surgical treatment and choosing the most effective drug treatment. Genome analysis of people with OI or their relatives can determine the possibility of OI in their child. Next generation sequencing (NGS) can be used to analyze the entire exome using panels with known genes responsible for OI [1, 7, 12].

Differential diagnosis of hereditary diseases of connective tissue is difficult in connection with the expressed clinical polymorphism and similarity of clinical displays at various diseases of this group. The exact diagnosis can be established on the basis of molecular genetic research, which in its turn will allow timely choice of tactics of the patient. Differential diagnosis is performed with other connective tissue dysplasias (Brooke's syndrome, Carpenter's syndrome, hypophosphatasia, Ehlers-Danlo syndrome, osteoporosis-pseudoglioma syndrome, idiopathic juvenile osteoporosis, etc.) [11].

Treatment of patients with OI is symptomatic and depends on the severity of the course. The goal of treatment is to reduce the frequency of fractures, increase mobility and independence, reduce pain, timely detection and control of extraskeletal manifestations, and prevention of drug therapy side effects. Patients with OI need a team multidisciplinary approach that includes a pediatrician, endocrinologist, rehabilitation specialist, orthopedic traumatologist, geneticist, dentist, audiologist, psychologist, and social worker [1, 7, 9, 12].

For many years (since 1987) the main method of therapy has been the use of bisphosphonates. The assessment of the dynamics of treatment with bisphosphonates is carried out by analyzing clinical and anamnestic data, the results of X-ray densitometry [6]. RANKL inhibitors, osteoanabolic drugs, including human parathyroid hormone analogues, sclerostin inhibitors, TGF inhibitors, and others are currently undergoing clinical trials. The main idea of cell replacement therapy is the transplantation of bone marrow or mesenchymal stem cells in order to obtain a pool of cells capable of producing collagen. The task of surgical treatment is timely and effective osteosynthesis of fractures, correction of deformities of long bones and scoliosis. Monitoring the course of the disease is carried out using radiological methods. Rehabilitation therapy consists in restoring the motor activity of patients after fractures and operations, which is the basis for maximum physical activity in patients with OI. Physical therapy should begin in early childhood and include aerobic exercise, muscle strengthening exercises, and walking protectors. Exercises to increase muscle strength (isotonic and anti-gravity, aerobic exercises) are performed between orthopedic interventions. Patients should also be encouraged to swim in the pool. Children and their parents need psychological support for social adaptation, as well as for learning to walk after correction and osteosynthesis of fractures. Correction of secondary diseases in OI, in particular, hearing loss, basilar intussusception, is carried out in specialized institutions according to the developed coordinated programs [1, 7, 9].

Clinical case

The child was born from the third desired pregnancy, which took place against the background of a threatened abortion at 8 and 14 weeks of gestation,

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diffuse non-toxic goiter of the 1st A degree, simple flat pelvis, oligohydramnios; third natural labor at 38 weeks of gestation. Outpouring of a small amount of amniotic fluid was noted; the anhydrous interval was 15 hours.

The first and second pregnancies ended with the birth of healthy children in the physiological gestational age. The hereditary history of the mother and father is aggravated by oncopathology.

The results of the screening antenatal ultrasound examination of the fetus at gestational age 33-34 weeks showed that the length of the limbs of the fetus corresponds to 25 weeks; no other abnormalities in the examination of the fetus were found. Also diagnosed with oligohydramnios and cord entanglement. A congenital malformation of the musculoskeletal system of the fetus is suspected: atelosteogenesis, which must be differentiated from campomelic dysplasia.

The child's body weight at birth was 2300 g, body length – 43 cm, head circumference – 31 cm, chest circumference – 29 cm. Apgar score at the end of the first minute of life – 6 points, the fifth minute of life – 7 points. At birth and in the early neonatal period, the child's condition was regarded as moderate due to moderate respiratory disorders, neurological symptoms in the form of depression syndrome and vegetative-visceral disorders against the background of small size before the gestational age and congenital pathology of the musculoskeletal system.

Phenotypically, congenital dwarfism with short limbs, small cartilaginous skull, hypertelorism, depressed nose bridge, micrognathia, and suspected campomelitic dysplasia were found.

After birth, an X-ray examination was performed to help identify fractures of the humerus.

During its stay in the neonatal intensive care unit of the obstetric hospital, the child was nursed in an open resuscitation system in compliance with the safety rules, received mechanical ventilation in the nIPPV/nCPAP mode with parameter correction; partial parenteral nutrition, tube-enteral nutrition; antibiotic therapy and pharmacological/non-pharmacological anesthesia. The child was consulted by specialist doctors: a geneticist, a neurologist, an orthopedist.

Based on the data of genetic, clinical and instrumental examination of the child, a preliminary clinical diagnosis was established: Osteogenesis Imperfecta. Parents were offered a molecular genetic study the results of which revealed a mutation c.2533G> A (p.Gly845Arg) of the COL1A1 gene.

Molecular genetic study of family members (mother, father and two sisters of the proband) did not reveal the pathological allele diagnosed in the proband. It can be assumed that the presence of a hereditary pathology of the musculoskeletal system in this child occurred as a result of a new mutation. After a comprehensive examination, the girl was diagnosed with osteogenesis imperfecta type III.

The family was given recommendations on prenatal diagnosis of the disease during subsequent pregnancy.

Conclusions

1. Significant genetic and phenotypic polymorphism of OI, the absence of genotype-phenotype correlation, similarity of clinical manifestations, and the complexity of diagnosis indicate the need for new generation sequencing technologies. 2. Currently, there are no standards for providing care to patients with OI, and each patient needs an individual approach when choosing drug therapy and planning surgical treatment. 3. Further studies are needed to focus on the effectiveness of long-term treatment and its impact on fracture risk in large cohorts of patients with different types of OI.

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КЛІНІЧНИЙ ВИПАДОК НЕДОСКОНАЛОГО ОСТЕОГЕНЕЗУ ІІІ ТИПУ, СПРИЧИНЕНИЙ МУТАЦІЄЮ ГЕНА COL1A1 (p.Gly845Arg), У НОВОНАРОДЖЕНОЇ ДІВЧИНКИ

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Резюме. Недосконалий остеогенез (НО) – захворювання, яке характеризується спадковою дисплазією сполучної тканини та клінічно проявляється у вигляді надмірної ламкості кісток та деформації кінцівок. Загальна частота НО становить 1:10 000-20 000 живонароджених. Встановлено основний аутосомно-домінантний шлях успадкування, аутосомно-рецесивні та Х-зчеплені форми, а також описані спорадичні випадки хвороби, мутації denovota сімейний мозаїцизм. У 85 % випадків мутації виникають в генах COL1A1 та COL1A2, що призводить до кількісних та якісних змін синтезу колагену І типу. Кількісні дефекти обумовлені формуванням нульового алеля, при якому структура колагену не змінюється, а його кількість знижується вдвічі. З якісних дефектів найбільш поширений тип мутації пов`язаний із заміною гліцину на амінокислоту більшого розміру. Це призводить до порушення процесу формування потрійного ланцюга та структурних змін молекули проколагену І типу.

У статті представлено клінічний випадок недосконалого остеогенезу ІІІ типу, спричинений мутацією гена COL1a1 (p.Gly845Arg), у новонародженої дівчинки. Антенатально діагностовано маловоддя та вкорочення кінцівок, після народження фенотипово виявлено вроджену карликовість з короткими кінцівками, малі розміри хрящового черепа, гіпертелоризм, втиснуте перенісся та мікрогнатію. При рентгенологічному обстеженні діагностовано переломи плечових кісток. Результати молекулярно-генетичного дослідження виявили мутацію c.2533G>A (p.Gly845Arg) генуCOL1A1.

Молекулярно-генетичне обстеження членів родини (мати, батько та дві рідні сестри пробанда) не виявило патологічного алеля, діагностованого у пробанда, тобто народження дитини зі спадковою патологією опорно-рухового апарату сталося в результаті нової мутації.

Ключові слова: незавершений остеогенез; мутація гена COL1a1 (p.Gly845Arg); мутація de novo.

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