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MOLECULAR-GENETICS ASPECTS, CLINIC AND DIAGNOSTICS OF ACHONDROPLASIA

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Achondroplasia (AP) (OMIM №100800) - a disease with an autosomal dominant type of inheritance with full penetrance, is detected at birth and is the most common cause of dwarfism. The prevalence of AP is 1:10 000-40 000 newborns, occurs equally often among men and women regardless of race. It is characterized by systemic skeletal lesions with impaired enchondral osteogenesis, dwarfism, respiratory lesions due to deformation of the chest and spine, shortening of the limbs at normal body length, deformation of the lower extremities [1,2,3].

AP occurs due to mutations in the gene FGFR3 (fibroblast growth factor receptor-3), which leads to a violation of the mechanism of enchondral ossification. The FGFR3 gene is located on the short arm of chromosome 4 (4p16.3), encodes a receptor for fibroblast growth factors type 3 and is responsible for the production of protein contained on the surface of cells belonging to various types of tissues, including cartilage. Normally, protein is responsible for signals from chemical compounds called growth factors that stimulate cell growth and maturation. AP –related FGFR3 mutations are function-enhancing mutations that cause independent activation of the FGFR3 protein. Such constant activation of the FGFR3 protein inhibits the proliferation of chondrocytes in the growth plate and leads to shortening of the tubular bones, as well as abnormal formation of other bones. 99% of cases of AP are caused by two mutations in which there is damage to the 1138 nucleotide of the FGFR3 gene with the replacement of guanine by adenine or cytosine. New mutations of guanine at the 1138 position of the FGFR3 gene occur exclusively in the germ cells of the father, their frequency increases with age of the father. Genetic aberrations in other parts of the FGFR3 gene lead to the development of milder forms of skeletal development, including hypochondroplasia [1]. In addition, FGFR3 mutations are associated with the emergence of phenotypes of other forms of dwarfism, which require differential diagnosis. [2-5].

Clinical manifestations. Already at birth in children with AP there is a lag in growth, the predominance of the cerebral part of the skull over the face, convexity of the forehead, saddle-shaped nose. All tubular bones are thickened, curved, tuberous, there is varus and valgus deformities, which progress with early loading of the lower extremities. Already in the first months of life you can see wide palms, shortened, almost the same length II-V fingers, the first finger longer than the others, a trident-shaped palm, wide and short hands and feet. Children suffering from AP, lag behind in physical development, late begin to hold his head (after 3 months), sit (after 8 months), walk (1.5-2 years). Already in the first year there is a kyphosis in the lumbar spine. As the child grows, the shortening of the limbs becomes more noticeable. For children suffering from AP, respiratory disorders are characteristic due to the peculiarities of the facial structure, large tonsils, small chest, which causes chronicity and inflammation of the respiratory system with a weak course and the development of respiratory failure. Patients are prone to obesity, especially in the elderly. The intellectual development of children does not suffer. Adult height does not exceed 130 cm for men and 124 cm for women. Life expectancy is close to normal [1,6,7].

Diagnosis is not difficult due to the pronounced abnormalities characteristic of the disease, as well as growth retardation. According to the recommendations of the American Academy of Pediatrics and Genetics (1995), the main in the examination and management of patients with AP are:

1. Anthropometry monthly during the first year of life, after a year – control of growth and circumference of the head using standardized curves for patients with AP.
2. Ultrasound of the brain.
3. Dynamic observation by a neurologist.
4. MRI/CT scan of the occipital foramen of the skull to assess the severity of hypotension or to exclude the possibility of spinal cord compression.
5. Consultations of a pediatric orthopedist with curvature of the limbs.
6. Consultations with a pediatric vertebrologist. Assessment of lumbar lordosis.
7. Observation of teething.
8. Consultations with a pediatric otorhinolaryngologist. Treatment of otitis in their occurrence.
9. Obtaining anamnestic data on the presence of apnea, if necessary – examination of the patient in the spring. With sleep apnea can be effective: adenotonsillectomy, weight loss (obesity), breathing mask and tracheotomy (in severe cases) [6].

X-rays of the skull, chest and tubular bones allow clarifying the nature of the pathology. For patients with AP on radiographs of the skull are characterized by: disproportion between the face and brain, reduction of the occipital foramen, enlargement of the mandible and skull bones, Turkish saddle in the form of a shoe, the base of the skull is flat and elongated; on X-rays of the chest there are thickened ribs, their deformation in the transition to the cartilaginous arch, kyphosis; on the radiograph of tubular bones – shortening and thinning of the diaphysis, thickening and cup-shaped expansion of the metaphysis, the pineal gland is pressed into the metaphysis by the type of hinges [2,3,5].

An important laboratory method of verifying the diagnosis of AP is molecular genetics research and determination of mutations in the FGFR3 gene [1,2-5].

Clinical case. Despite the accumulated knowledge about AP, the diagnosis in some cases causes some difficulties. A mother and 7-year-old daughter sought medical help from an endocrinologist for her child's short stature.

A girl from the second pregnancy, who was on the background of the threat of miscarriage and chronic placental insufficiency. Mother 26 years old, secondary education, works as a seamstress, work is associated with significant physical activity (long, sedentary). Father 40 years old, secondary education, handyman. The mother smokes for a long time. Heredity through mother and father is burdened by cardiovascular pathology. Paternal grandfather had a short stature. Prenatal ultrasound during pregnancy, according to the mother, did not reveal any pathology. Childbirth at 40 weeks. Birth weight 3100, length – 52 cm. Child's height at 1 year – 72 cm (+20 cm/year), at 5 years – 84 cm (+3 cm/year), now – 101 cm (norm is 114-125 cm), indicating a growth retardation of 3 sigma deviations. The child's weight is 19 kg. An endocrinologist suspected hypochondroplasia and recommended an examination by a pediatric orthopedist and a geneticist. An orthopedist diagnosed achondroplasia with a deficiency of tubular bone growth and sent for an X-ray examination of the hip joints, which revealed Blount's disease. According to the radiograph of the hands revealed: shortening of the diaphysis of the I-V metacarpal bones; shortening of the proximal, middle and distal phalanges of both hands; thickening and deformation of the head I-V of the metacarpal bones, with a sparse bone structure; radial bones arched medially; ulnae curved laterally; achondroplasia of both hands was established.

Examination by a geneticist revealed a protruding forehead, macrocephaly, hypoplasia of the middle part of the face, shortening of the proximal segments of the extremities, a trident-shaped hand, brachydactyly. Achondroplasia was suspected, and a molecular genetic study was detected, which revealed a pathogenic mutation of p.11138G>A(p.Gly380Arg) of the FGFR gene, which allowed to verify the diagnosis of achondroplasia. It was also found that child is a carrier of autosomal recessive states associated with the WDR34 gene, which is associated with short-rib thoracic dysplasia (SRTD). The girl was taken under medical supervision and a set of diagnostic and rehabilitation measures was prescribed. The family was given recommendations for planning the next pregnancy and prenatal diagnosis. For healthy parents of a child with AP, the risk of giving birth to the next child with short stature is low, but higher than in the general population. Prenatal diagnosis up to the 20th week of gestation is possible only with molecular testing of the fetus. At the end of pregnancy, the diagnosis can be established by radiography of the fetal bones.

Comprehensive examination of the child with detailed data of anthropometry, clinical and genealogical anamnesis of life, syndromic diagnosis, as well as molecular genetic research are important for the timely diagnosis of systemic skeletal diseases.

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