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THANATOPHORIC DYSPLASIA: LITERATURE REVIEW AND CLINICAL CASE IN MONOCHORIC DIAMNIOTIC TWINS

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Summary

Thanatophoric dysplasia, TD (OMIM: 187600, 87601) belongs to the group of FGFR3 chondrodysplasias and is divided into types I and II. The incidence of TD is approximately 1:20,000-50,000 newborns. TD is usually caused by pathogenic variants in the FGFR3 gene, which provides instructions for making a protein involved in the development and maintenance of bone and brain tissue. Mutations in the gene result in excessive protein activity. TD is inherited as an autosomal dominant trait, although cases of autosomal recessive inheritance have been described.

According to the radiologic changes of the bones and skull, there are 2 clinical types of TD: type I (TD1, MIM 187600) and type II (TD2, MIM 187601) with some overlap between them. Type I TD is characterized by micromelia with curved femurs, marked platyspondylia with or without a cloverleaf skull. TD type II is characterized by micromelia with straight femurs and the uniform presence of moderate to severe craniosynostosis with a leaf-shaped skull deformity due to premature closure of the coronal and lambdoid sutures..

The diagnosis of TD is made syndromologically and/or radiologically and/or by detection of a heterozygous pathogenic FGFR3 variant identified by molecular genetic testing.

The article presents a rare clinical case of TD in monochorionic dizygotic twins with a fatal outcome. During prenatal ultrasound examination at 26-27 and 35-36 weeks of gestation, signs of skeletal dysplasia were diagnosed in both fetuses against the background of pronounced polyhydramnios. It should be noted that the father of the children is over 60 years old.

The diagnosis of both children was made syndromologically and radiologically based on the detection of phenotypic signs of TD (predominance of the skull over the face, short upper and lower limbs, altered shape of the chest, inflamed nasal bridge) and radiological signs of TD (short ribs, narrow chest, relative macrocephaly, micromelia of all limbs). Genetic testing for TD was not performed.

The clinical case was published with the consent of the parents in accordance with the principles of bioethics.

Key words: *Thanatophoric Dysplasia; Fibroblast Growth Factor Receptor 3; Monochorionic Diamniotic Twin.*

Introduction

Skeletal dysplasia (SD) is a diverse group of disorders that affect bone development and morphology. More than 456 different diseases are known, divided into 40 categories according to their main characteristics (radiologic findings, molecular etiology, mode of inheritance) and caused by mutations in more than 430 genes. Of these, 40% can be detected in the perinatal period, accounting for 9 deaths per 1000 births [1]. The most common lethal DMs are thanatophoric dysplasia and the achondrogenesis group, which account for 40-60% of all cases [1, 2].

Thanatophoric dwarfism was first described in 1967 by Pierre Marot and colleagues using the Greek term «thanatophoric» meaning «deadly» [3, 4]. In 1977, at the Second International Conference on the Nomenclature of Skeletal Dysplasias, this term was replaced by thanatophoric dysplasia (TD) (OMIM: 187600, 87601). Currently, according to the international nomenclature, TD belongs to the first group – the group of *FGFR3* (fibroblast growth factor receptor 3) chondrodysplasias and is divided into type I and type II [5].

FGFR3-related skeletal dysplasia is a relatively common subset [6]. The incidence of TD is about 1:20,000-50,000 newborns [7]. In a population study, Andersen and Hauge found a prevalence of 3.8:100,000 births. Other population-based studies report a prevalence ranging from approximately 1.1:100,000 births in Japan to 2.1-3.0:100,000 births in the United States [5, 8]. Type I TD is more common (80% of all cases) than type II TD, and accounts for 1:20,000-40,000 stillbirths and live births (MIM 187600) or 1:33,000-47,000 live births [9, 10].

TD is usually caused by pathogenic variants in the *FGFR3* gene, which provides the instructions for making a protein involved in the development and maintenance of bone and brain tissue, and *FGFR3* is the only gene whose mutation leads to TD. Mutations in the gene lead to excessive protein activity, resulting in impaired bone growth due to premature ossification [11, 12]. It is not known how *FGFR3* mutations cause the brain and skin abnormalities associated with this disorder. [5, 7].

The *FGFR3* gene has been mapped to chromosome 4p16.3 and consists of 19 exons spanning 16.5 kb [11, 13]. All cases were sporadic except for an exceptional paternal germline mosaicism [14]. Mutations in the *FGFR3* gene are associated with older paternal age [7]. If the father is old, there is a higher risk of new mutations (de novo) compared to the mother's age due to the high number of cell divisions during spermatogenesis [1].

More than 50% of patients with type I TD and 100% with type II TD have mutations in the *FGFR3* gene. TD type I is associated with a mutation in the extracellular domain of *FGFR3*, and TD type II is associated with a mutation in the intracellular domain of the tyrosine kinase.

In TD type I, cysteine replaces several amino acids in three separate regions of the extracellular domain. These mutations cause activation of the receptor. It is interesting to note that if cysteine replaces amino acids located in

different places, this causes different intensity of activation and leads to a less severe form of dwarfism, for example, achondroplasia. This suggests that the intensity of *FGFR3* activation depends on the position.

In TD type I, the extracellular arginine at position 248 of the protein is replaced by cysteine [16]. To date, 3 mutations responsible for TD type I1 are known: R248C (c.742C>T), Y373C (c.1118A>G), and S249C. The most common is the R248C mutation, which occurs in 50% of TD type I cases, followed by the Y373C mutation, which occurs in 20% of cases [9]. Both mutations result in cases with more severe radiologic manifestations than TD type I due to R248C.

In 2014, Xue et al. reported an update from ISDR in which mutation analysis included sequencing of the entire coding region in 324 cases, including achondroplasia and hypochondroplasia. It was found that 90% of TD type I mutations were pArg248Cys or pTyr373Cys. The third most common was the stop codon mutation pX807 and the fourth was pSer249Cys. The pGlu370Cys mutation was 2.3% and the pLys650Met mutation was 1.2%. This information is useful in the design and costing of commercial tests for TD type I [9].

Other data have reported 10 FGFR3 gene mutations causing TD type I, which are either missense codon mutations or stop codon mutations (p.X807G (c.2419T>G); p.x807R (c.2419T>A); p.X807C (c.2421A>T)); the latter lead to protein elongation [9, 13, 15].

Type II TD is associated with a single mutation (K650E, also known as p.Lys650Glu) in the intracellular tyrosine kinase domain, which replaces lysine with glutamic acid at position 650 in one of the intracellular subdomains of FGFR3 [4, 8]. In patients with this replacement, the femurs are straight and the skull has a cloverleaf shape. In other mutations, the femurs are curved. The mutation has 100% penetrance and shows better preservation of the growth plate compared to TD type I [8, 9].

Mutations lead to activation of *FGFR3* by various mechanisms. Extracellular FGF ligands form dimers. The TD type I mutation Y373C forms covalently bound dimers between cysteine residues near the juxtamembrane domain. Amino acid substitutions in the intracellular domain, such as K650M in TD type I / SADDAM or K650E in TD type II, mimic conformational changes leading to dimerization and autophosphorylation [9]. Low levels of activity require FGF ligand for activation: high levels of activity, as seen with the R248C and Y373C mutations, result in spontaneous dimerization and are ligand-independent. Other amino acid substitutions cause varying degrees of *FGFR3* activation, resulting in varying degrees of chondrocyte inhibition. The most severe inhibition results in the most severe degree of skeletal dysplasia. In the absence of mutation, inhibition of chondrocytes by *FGFR3* can be considered as aging [9].

TD is inherited as an autosomal dominant trait; cases of autosomal recessive inheritance have also been described. Autosomal dominant inheritance is confirmed by the presence of abnormalities in monozygotic twins [16]. The risk of recurrence in siblings of parents who have had an affected child is not significantly increased. Germline mosaicism in healthy parents, although not yet reported, remains a theoretical possibility.

Fibroblast growth factors (FGFs) and FGF receptors (FGFRs) play an important role in the development of the human axial and craniofacial skeleton. *FGFR3* is a physiological negative regulator of bone growth, inhibiting chondrocyte proliferation and differentiation and promoting chondrocyte apoptosis [8]. The inhibitory role of *FGFR3* in cartilage is unique compared to its aberrant signaling in other tissues.

FGFR3 is a membrane-bound receptor protein composed of extracellular immunoglobulin-like domains, a transmembrane domain, and intracellular (TK) domains. Binding of various FGFs to FGFR3 induces receptor dimerization and transphosphorylation of tyrosine residues, leading to the activation of several downstream signaling pathways, including mitogen-activated protein kinase (MAPK) cascades. Under normal conditions, *FGFR3* regulates the proliferation, differentiation and development of cells in the bones and cerebral cortex. Enhancement of *FGFR3* function activates TK, which can cause various abnormalities of the brain, for example, the normal cell cycle, differentiation and proliferation of chondrocytes are disturbed, which prevents endochondral ossification of long bones and their proper longitudinal growth [4, 15].

Loss of *FGFR3* function causes excessive growth of long bones in *FGFR3* knockout mice and individuals with CATSHL syndrome, confirming the important role of *FGFR3* as a negative regulator of bone growth [6].

Pathogenic variants of the *FGFR3* gene are responsible for a group of chondrodysplasias characterized by shortened limbs, macrocephaly, and a narrow chest. Since the discovery of the mechanism of *FGFR3* activation as a genetic cause of achondroplasia (ACH) in 1994, the pathogenesis of other disorders also caused by increased *FGFR3* function has been elucidated: hypochondroplasia (HCH), thanatophoric dysplasia, and severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) [6].

Delezoide and others proposed the pathomechanism of TD through experimental studies and concluded that the constitutive activation of *FGFR3* in cartilage by forming a stable dimer contributes to its translocation to the nucleus where it prevents the final differentiation of chondrocytes [15].

According to the radiological changes of bones and skull, there are 2 clinical types of TD: type I (TD1, MIM 187600) and type II (TD2, MIM 187601) with some overlap between them [12].

Type I TD is characterized by micromelia with curved femurs, pronounced platyspondylia with or without a cloverleaf skull [13].

Type II TD is characterized by micromelia with straight femurs and the uniform presence of moderate and severe craniosynostosis with cloverleaf-like skull deformation due to premature closure of the coronal and lambda-like sutures [4, 7, 13, 17, 18, 19, 20].

General skeletal manifestations are much more severe in TD type I, while severe craniosynostosis is associated with type II [14]. Some features common to both types are micromelia, short ribs, narrow chest, macrocephaly, characteristic facial features, brachydactyly, hypotonia, excess skin folds on the extremities, hypoplastic iliac bones, unhardened pubic bone, narrow sacro-gluteal notch [4]. With both types of TD, the vertebral bodies can have

a «U» or «H» format; the ribs are thin and small, which reduces the volume of the chest and leads to hypoplasia of the lungs. Usually, the liver is large and becomes the main site of hematopoiesis [5].

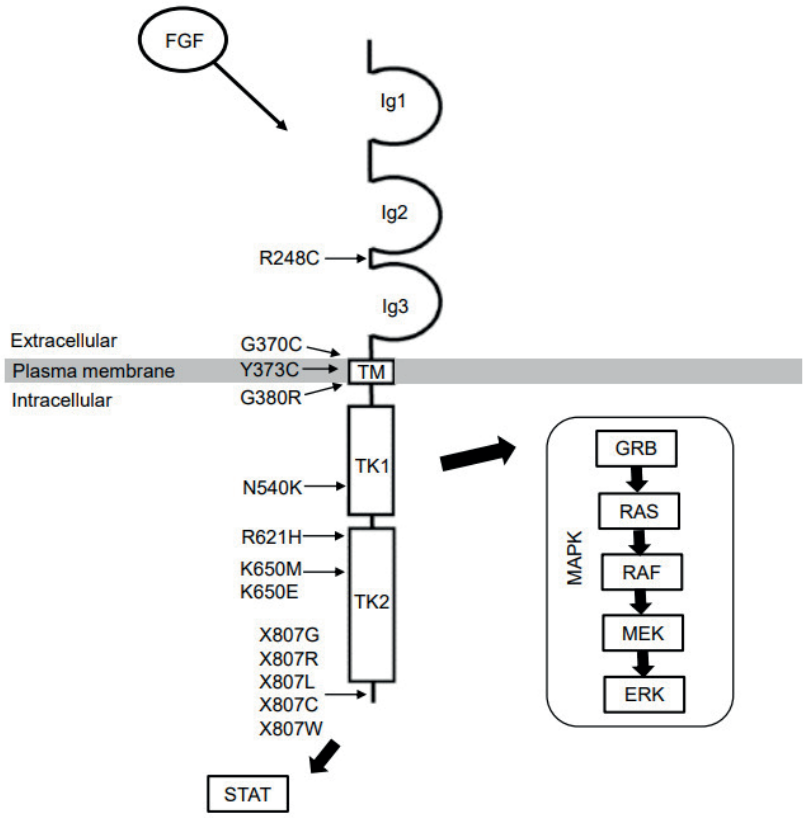

Fig. 1. Human FGFR3 protein structure and FGFR3 signal transduction. Positions of the representative pathogenic variants in the FGFR3 gene are indicated. Ig, immunoglobulin-like domain; TM, transmembrane domain; TK, tyrosine kinase domain; STAT, signal transducer and activator of transcription; MAPK, mitogen activated protein kinase [6]

One of the early reports of neuropathological findings in TD was described by Goutieres et al. in 1971. Abnormalities of the temporal lobe gyri, hippocampal dysplasia, and polymicrogyria were reported in the temporal cortex of two infants [4]. The most common brain abnormalities are hypoplasia of the posterior cranial fossa, megalencephaly, hippocampal abnormality, gyrus disorganization, neuronal heterotopias, and dysplasia of the inferior olive, but these are nonspecific. Neural changes occur before the process of ossification entails a limitation in the size of the meninges. It is likely that nerve abnormalities in TD are internal defects of the nervous system [5].

In addition to changes on the part of the skull and limbs in TD, it was also reported about the combination of the disease with horseshoe-shaped deformation of the kidneys, hydronephrosis, atrial membrane defect, tricuspid valve defect, anus atresia, radioulnar synostosis, open ductus arteriosus, underdevelopment of the inferior olive and dentate nuclei of the cerebellum [11, 21, 22].

The diagnosis of TD is established syndromologically and/or radiologically and/or by establishing a heterozygous pathogenic *FGFR3* variant identified during molecular genetic testing. In a study conducted from 2010 to 2014, patients with suspected TD participated in an epidemiological program of congenital malformations called the Latin American Collaborative Study of Congenital Malformations (ECLAMC, Portuguese abbreviation). Clinical and radiological studies, as well as photographs, were evaluated when available based on the methodology modified by Barbosa-Buck et al. Three different levels of diagnostic evidence (DEL) were established: DEL-1 (good radiographic quality and/or positive genotype and/or further clinical information establishing the diagnosis); DEL-2 (satisfactory characteristics of clinical and radiological examination to establish one or more probable diagnoses); and DEL-3 (clinical data and images of sufficient quality to be classified as TD) [1].

Radiographic features include [2]:

a) the proximal parts of the long limbs are short and have a rhizomelic appearance.

Long limbs (as a rule, humerus and femur) have the appearance of a telephone receiver (curved with a metaphyseal extension);

b) iliac bones are usually hypoplastic, the wing of the iliac bone has a small square shape, the roof of the acetabulum is in the form of a «trident»;

c) the chest is narrow, and the ribs are short, horizontal; shoulder blades small;

d) relative macrocephaly with a protruding frontal bone, flattening of the bridge of the nose and cloverleaf skull (with type II TD);

e) platyspondylia (flattening of the vertebral body).

The gold standard for prenatal verification of TD, as for most skeletal dysplasias, is currently molecular genetics. The material can be obtained by amniocentesis, which is usually performed at 15-18 weeks of pregnancy, or by chorionic biopsy (approximately at 10-12 weeks of pregnancy) [18]. Moreover, the molecular genetic method can be the only criterion when it comes to termination of pregnancy or when there is no possibility to conduct a pathomorphological examination [11, 18].

The lethal nature of TD necessitates prenatal diagnosis of this pathology. The diagnosis of TD can be made in utero using ultrasound diagnostics and immediately after birth on the basis of clinical examination (syndromological), portrait diagnosis, radiological studies, histopathology and molecular analysis [23, 24].

Usually, prenatal ultrasound (US) allows the diagnosis of TD to be made after 20 weeks. [11]. In 71% of cases, TD is associated with polyhydramnios, which is so pronounced that it may cause preterm delivery. Motor activity of the fetus apparently does not suffer in this disease, but it is reported to decrease in the third trimester of pregnancy. Against the background of signs of osteochondrodysplasia, such as micromelia, narrow chest, and macrocephaly, the pathognomonic signs of TD are shortened femurs in the shape of a telephone tube (type I) and the shape of the skull in the shape of a trefoil (type II). In both types, there is increased transparency of the occipital bone in the first trimester, ventriculomegaly, agenesis of the corpus callosum, congenital heart defects, and hydronephrosis [13].

Sonographic signs may include: a) relatively narrow chest cavity; b) short, thick, curved tubular bones, especially in the lower limbs; c) thickening of the soft tissues of the limbs; d) relatively large head with frontal protrusion; e) cloverleaf-shaped skull in type II TD. Detection of typical features of TD by ultrasound (US) allows for diagnosis, but diagnostic accuracy is reported to be variable, ranging from 40-88% [15].

In cases of prenatal diagnosis of TD, the goal is to avoid potential pregnancy complications, including preterm delivery, polyhydramnios, malpresentation, and labor complications due to macrocephaly and/or cervical flexion and rigidity. Cephalocentesis and cesarean section may be considered to avoid maternal complications. The possibility of selective intrauterine termination with the possibility of prolonging a normal singleton pregnancy is reported in the case of TD in one of the twins, which was prenatally diagnosed by DNA analysis after amniocentesis at 15 weeks [22, 25, 26].

It should be noted that multiple pregnancy with twins, especially with monozygotic twins, significantly increases the overall risk of congenital anomalies. They can occur in both dichorionic and monochorionic twins. Discordant anomalies caused by genetic disorders have been described mainly in dizygotic twins, but rarely in a pair of monozygotic twins [16]. Overall, it has been estimated that both twins have the same abnormality in about 15% of cases. Sporadic cases of thanatoform dysplasia in fetuses and children in multiple pregnancies have been described in the literature [27, 28].

The differential diagnosis of TD should include imperfect osteogenesis type II, characterized by fractures of long bones, and achondrogenesis, characterized by extreme hypomineralization but without the classic multiple skin folds [8, 18, 29]. The differential diagnosis also includes Ellis-Van Creveld syndrome (chondroectodermal dysplasia), asphyxial thoracic dysplasia, chondrodysplasia syndrome with polydactyly, severe hypophosphatasia, and homozygous achondroplasia [19, 31].

Differential diagnosis with the above mentioned homozygous achondroplasia can be difficult only by clinical and radiologic signs. In the heterozygous form of achondroplasia, the tubular bones are only slightly shortened and not curved. The ratio of femur length to biparietal size becomes abnormal after 21-27 weeks of gestation. In thanatophoric dysplasia, on the other hand, the micromelia can be so pronounced that in some cases they can be detected as early as the 19th week of pregnancy.

Asphyxial dysplasia of the chest can be differentiated by less pronounced shortening of the bones and preservation of the vertebral bodies. Prenatal radiography of the fetal spine is helpful in diagnosis. Real-time ultrasound may be used to select the correct plane for radiologic examination of the spine. TD is characterized by an H-shaped configuration of the vertebral bodies.

Chondroectodermal dysplasia is characterized by a correctly formed extra digit and an acromelic-type shortening of the limb. Fibrochondrogenesis is characterized by dumbbell-shaped metaphyses.

Such a large number of syndromes and the complexity of differential diagnosis are the reason for molecular analysis of TD to establish an accurate diagnosis.

Intrauterine death usually results from severe respiratory failure due to reduced thoracic volume and lung hypoplasia and/or respiratory failure due to brainstem compression [11].

Most affected infants die of respiratory failure shortly after birth. The cause of death is cardiovascular and respiratory failure, probably associated with a decrease in chest volume [24]. Neonates usually require long-term respiratory support. Aggressive ventilatory support and surgical decompression of the trachea, followed by comprehensive physical rehabilitation, can lead to long-term survival [8]. However, they have severe psychosocial and physical disabilities and require extensive respiratory and nutritional support. Rare cases of prolonged survival, often dependent on mechanical ventilation, with marked growth failure and intellectual disability have been reported [6, 31].

Management goals should be established with the family and may focus on comfort care. Neonates require prolonged respiratory support. Recommendations for the administration of anesthesia for skeletal dysplasia apply to individuals with TD. Other treatments may include shunting for hydrocephalus, suboccipital decompression to relieve craniocervical stenosis, anticonvulsants to control seizures, and hearing aids.

C-type natriuretic peptide (CNP) is a potent positive regulator of endochondral bone growth. Studies have shown that plasma CNP levels are altered in FGFR3 pathies. Clinical trials of CNP analogues in children with achondroplasia are currently underway. Initial results have shown a moderate increase in growth. There are also several other potential therapeutics for achondroplasia

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under investigation. These drugs will also benefit children with TD in the future [3].

Surviving patients require neuroimaging to monitor craniocervical stenosis, assessment of neurologic status, and EEG to monitor seizure activity, as well as developmental and audiologic evaluations.

Clinical Case. The article presents a rare case of thanatophoric dysplasia in monochorionic diamniotic twins with a fatal outcome. The clinical case was published with the consent of the parents in accordance with the principles of bioethics.

Children born from the 3rd pregnancy with monochorionic diamniotic twins (MCDAT), from the 3rd delivery at 36 weeks by cesarean section due to MCDAT and breech presentation of both fetuses. The pregnancy was complicated by progressive polyhydramnios and maternal obesity of 2nd degree. This pregnancy was a natural, unplanned pregnancy. The pregnant woman was registered at the maternity clinic.

During the prenatal ultrasound examination, signs of skeletal dysplasia of both fetuses were diagnosed against the background of pronounced polyhydramnios (at the gestational age of 26-27 weeks, the length of the limbs of both fetuses corresponded to 17-18 weeks, at the gestational age of 35-36 weeks – to 20-21 weeks), as well as cardiomegaly in the II fetus.

During the interview with the parents of the children it was found out that before and during pregnancy the mother worked under strenuous physical conditions, with synthetic materials, and the father – with paints and other construction materials. In addition, the father belongs to the older age group of the population (> 60 years). Heredity on the mother's side is burdened by the presence of cardiovascular pathology, on the father's side it is not. Deny harmful habits. Previous pregnancies resulted in the birth of two healthy children.

The first child was born with a body weight of 2200 g, body length of 39 cm, head circumference of 36 cm, chest circumference of 30 cm. Apgar score at the end of the first minute was 3 points, at the fifth minute – 5 points, at the tenth minute – 7 points. Resuscitation measures were carried out, including artificial ventilation of the lungs through an intubation tube.

The second child was born with a body weight of 2200 g, body length of 39 cm, head circumference of 35 cm, chest circumference of 29 cm. Apgar score at the end of the first minute was 2 points, at the fifth minute – 5 points, at the tenth minute – 5 points. Resuscitation measures were also carried out, including artificial ventilation of the lungs through an intubation tube.

During the external examination of both children, phenotypic signs of a disturbance in the formation of the locomotor system were noted, namely, the predominance of the cerebral skull over the facial skull, short upper and lower limbs, a changed shape of the chest, inflamed bridge of the nose, etc. (Fig. 2).

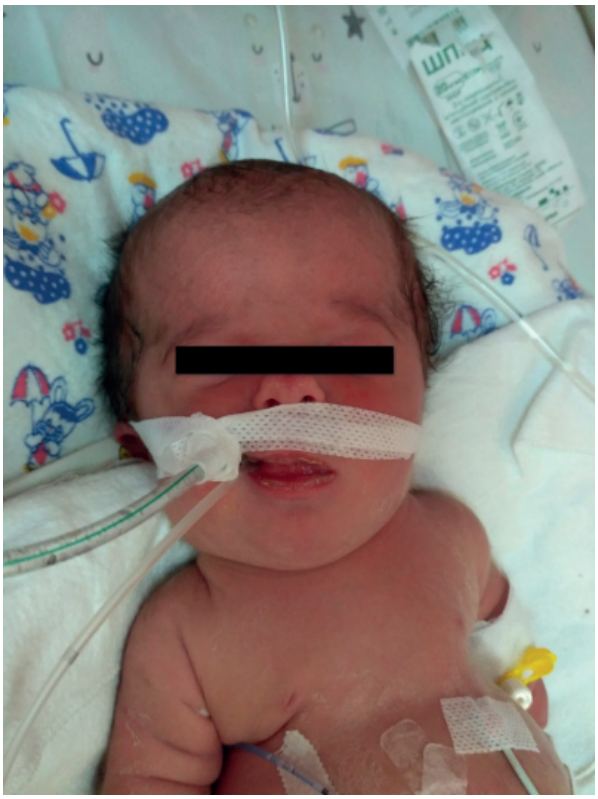

Fig. 2. Phenotype of the second child from twins

When assessing physical development according to percentile tables, it was established that children's body weight corresponds to the 25th percentile, height is below the 10th percentile, and head circumference is above the 90th percentile. When assessing gestational age according to the new Ballard scale, children's development corresponds to 34 weeks of gestation.

X-ray examination of children revealed short ribs, narrow chest, relative macrocephaly, micromelia of all limbs (Figs. 3, 4).

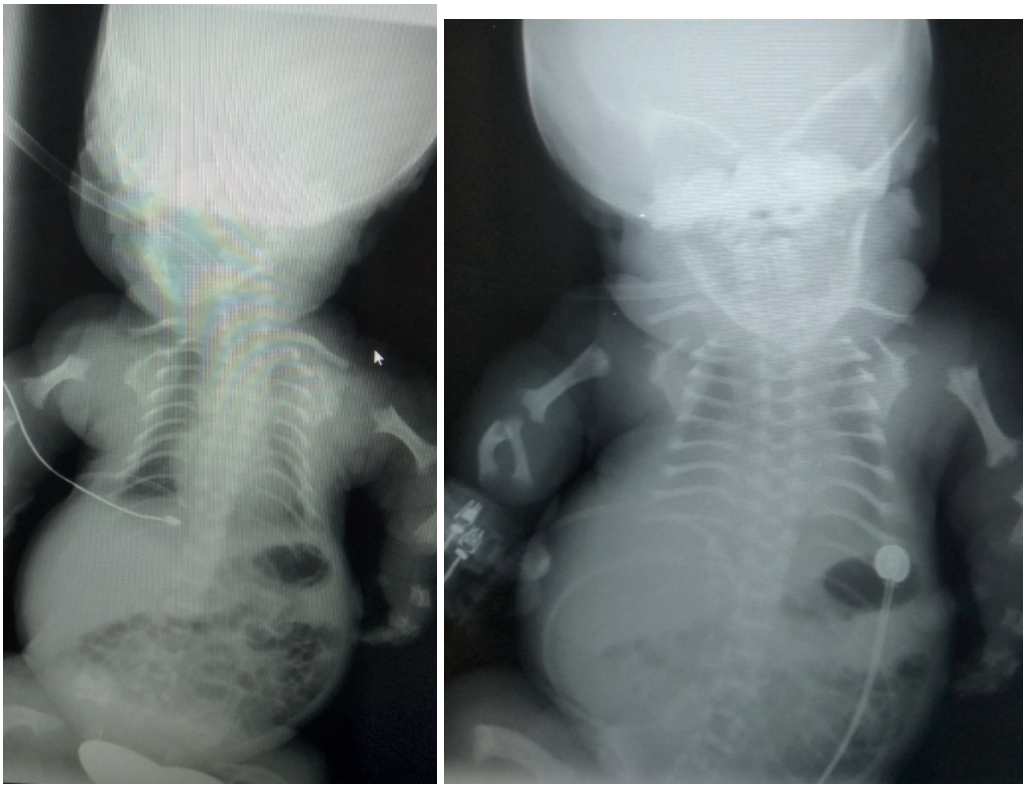

Fig. 3, 4. X-ray images of the first and second child

The condition at birth and throughout the life of both children is severe with gradual negative dynamics due to manifestations of multiple organ failure syndrome with damage to the respiratory system (respiratory failure III degree), nervous system (coma III-IV degree), cardiovascular system (circulatory insufficiency III degree), and others. Both children were also diagnosed with congenital malformation of the central nervous system – pachygyria, as well as lung hypoplasia. During their life the children developed secondary pulmonary hypertension, anemia of prematurity and internal hydrocephalus.

The children received complex intensive care and later palliative care in the conditions of the intensive care unit. From the moment of birth, the support of vital functions was provided by artificial lung ventilation, infusion therapy with parenteral nutrition, inotropic support, antibiotic therapy, complex analgesic therapy, etc. The children were brought up in safe conditions, with constant contact with their parents. The first child lived for 4 months, the second for 2 months and 16 days. The parents refused to have the children autopsied.

Both children were diagnosed with thanatophoric dysplasia on the basis of phenotypic and radiological signs. The parents refused molecular genetic examination for TD. Achondroplasia was excluded by the DNA method of research.

Conclusions

1. Thanatophoric dysplasia (TD) is a form of chondrodysplasia caused by pathogenic changes in the *FGFR3* gene, which controls protein synthesis for the development and maintenance of bone and brain tissue. The incidence is about 1:20,000-50,000 newborns, it is usually inherited in an autosomal dominant pattern and is closely related to the older age of the father.

2. The diagnosis of TD is established syndromologically and/or radiologically and/or by detection of a heterozygous pathogenic variant of *FGFR3*. Typical features are micromelia with curved (type I) or straight (type II) femurs, pronounced platyspondylia with or without a cloverleaf skull, short ribs, narrow chest, macrocephaly, characteristic facial features, brachydactyly, hypotonia, excess folds skin on the limbs, hypoplastic iliac bones, unhardened pubic bone, narrow sacro-gluteal notch, etc.

3. Differential diagnosis of TD is carried out with osteogenesis imperfecta type II, Ellis-Van Creveld syndrome (chondroectodermal dysplasia), asphyxic dysplasia of the chest, chondrodysplasia syndrome with polydactyly, severe hypophosphatasia and homozygous achondroplasia. The prognosis for children with TD is often unfavorable, they require long-term multidisciplinary intensive/palliative care.

4. The authors of the article presented a rare clinical case of TD in monochorionic diamniotic twins with a fatal outcome. Both children were diagnosed syndromologically and radiologically on the basis of phenotypic (predominance of the cerebral skull over the facial, short upper and lower limbs, changed shape of the chest, inflamed bridge of the nose) and radiological (short ribs, narrow chest, relative macrocephaly, micromelia of all limbs) findings. signs of TD. Genetic examination for TD was not carried out.

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ТАНАТОФОРНА ДИСПЛАЗІЯ: ОГЛЯД ЛІТЕРАТУРИ ТА КЛІНІЧНИЙ ВИПАДОК У МОНОХОРІАЛЬНИХ ДІАМНІОТИЧНИХ ДВІЙНЯТ

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Резюме

Танатофорна дисплазія, ТД (OMIM: 187600, 87601) відноситься до групи хондродисплазій *FGFR3* і поділяється на I та II тип. Захворюваність на ТД становить біля 1:20000-50000 новонароджених. ТД зазвичай спричинена патогенними варіантами в гені *FGFR3*, який забезпечує інструкції для створення білку, що бере участь у розвитку та підтримці кісткової і мозкової тканини. Мутації в гені призводять до надмірної активності білка. Успадковується ТД за аутосомно-домінантним типом, хоча описані випадки з аутосомно-рецесивним успадкування.

Відповідно до рентгенологічних змін кісток та черепа, існує 2 клінічних типи ТД: тип I (TD1, MIM 187600) та тип II (TD2, MIM 187601) з деяким перекриттям між ними. ТД I типу характеризується мікромелією з викривленими стегновими кістками, вираженою платиспондилією з черепом у вигляді листка конюшини або без нього. ТД II типу характеризується мікромелією з прямими стегновими кістками та рівномірною наявністю помірного та тяжкого краніосиностозу з деформацією черепа у вигляді листка через передчасне закриття вінцевих і ламбдоподібних швів.

Діагноз ТД встановлюється синдромологічно та/або радіологічно та/або виявленням гетерозиготного патогенного варіанту *FGFR3*, ідентифікованим під час молекулярно-генетичного тестування.

У статті представлено рідкісний клінічний випадок ТД у монохоріальних діамніотичних двійнят з летальним виходом. При проведенні пренатального УЗ-обстеження у терміні гестації 26-27 та 35-36 тижнів діагностовано на фоні вираженого багатоводдя ознаки скелетної дисплазії обох плодів. Слід відмітити, що батько дітей старше 60 років.

Діагноз у обох дітей встановлено синдромологічно та радіологічно на основі виявлення фенотипічних ознак ТД (переважання мозкового черепа над лицьовим, короткі верхні та нижні кінцівки, змінена форма грудної клітини, запале перенісся) та рентгенологічних ознак ТД (короткі ребра, вузька грудна клітина, відносна макроцефалія, мікромелія усіх кінцівок). Генетичне обстеження на ТД не проведено.

Клінічний випадок опубліковано за згодою батьків з дотриманням принципів біоетики.

Ключові слова: танатофорна дисплазія; рецептор фактора росту фібробластів 3; монохоріальна діамніотична двійня.

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