УДК 616-055.5/.7-053.2(048.8)
https://doi.org/10.17816/PTORS16047

LOEYS–DIETZ SYNDROME (literature review and case description)

© ***O.E. Agranovich[1], S.Yu. Semenov[2], E.F. Mikiashvili[1], S.V. Sarantseva[3]***

[1] H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery, Saint Petersburg, Russia;
[2] Children's City Hospital No. 22, Saint Petersburg, Russia;
[3] Petersburg Nuclear Physics Institute named by B.P. Konstantinov of National Research Centre "Kurchatov Institute", Saint Petersburg, Russia

■ For citation: Agranovich OE, Semenov SYu, Mikiashvili EF, Sarantseva SV. Loeys–Dietz syndrome (literature review and case description). *Pediatric Traumatology, Orthopaedics and Reconstructive Surgery*. 2020;8(1):83-94. https://doi.org/10.17816/PTORS16047

Received: 14.09.2019 Revised: 15.11.2019 Accepted: 10.03.2020

Background. The Loeys–Dietz syndrome is a rare autosomal dominant connective tissue disorder characterized by the pathology of the cardiovascular system in combination with various anomalies of the musculoskeletal system. In modern literature, there is neither any information about the frequency of pathology nor any algorithm of examination and treatment for patients with this syndrome.
Clinical case. The article presents a clinical observation of a 7-year-old patient with Loeys–Dietz syndrome with a genetically confirmed diagnosis.
Discussion. This article provided a literature review, examined diagnosis issues and differential diagnosis, and presented the clinical picture of the syndrome. The main symptoms of Loeys–Dietz syndrome are artery aneurysms (most often in the aortic root), arterial tortuosity (mainly the vessels of the neck), hypertelorism, and bifid (split) or broad uvula. However, the combination of these symptoms is not found in all patients with this disease.
Conclusions. The article emphasized the importance of a genetic verification of the disease, as well as a multidisciplinary approach to treatment with mandatory dynamic monitoring by specialists such as a cardiologist, neurologist, orthopedist, and pediatrician, which help prevent the development of complications and increase the life expectancy of this group of patients.

Keywords: Loeys–Dietz syndrome; aneurysm and dissection of the aorta; generalized tortuosity of the artery; transforming growth factor-β.

СИНДРОМ ЛОЕСА – ДИТЦА (обзор литературы и описание клинического случая)

© ***О.Е. Агранович[1], С.Ю. Семенов[2], Е.Ф. Микиашвили[1], С.В. Саранцева[3]***

[1] Федеральное государственное бюджетное учреждение «Национальный медицинский исследовательский центр детской травматологии и ортопедии имени Г.И. Турнера» Министерства здравоохранения Российской Федерации, Санкт-Петербург;
[2] Государственное бюджетное учреждение здравоохранения «Детская городская больница № 22», Санкт-Петербург;
[3] Федеральное государственное бюджетное учреждение «Петербургский институт ядерной физики им. Б.П. Константинова» Национального исследовательского центра «Курчатовский институт»

■ Для цитирования: Агранович О.Е., Семенов С.Ю., Микиашвили Е.Ф., Саранцева С.В. Синдром Лоеса – Дитца (обзор литературы и описание клинического случая) // Ортопедия, травматология и восстановительная хирургия детского возраста. – 2020. – Т. 8. – Вып. 1. – С. 83–94. https://doi.org/10.17816/PTORS16047

Поступила: 14.09.2019 Одобрена: 15.11.2019 Принята: 10.03.2020

Обоснование. Синдром Лоеса – Дитца — редкое аутосомно-доминантное заболевание соединительной ткани, характеризующееся патологией со стороны сердечно-сосудистой системы в сочетании с различными аномалиями опорно-двигательного аппарата. В современной литературе нет данных о частоте встречаемости патологии, а также не описан алгоритм обследования и лечения пациентов с данным синдромом.

Клиническое наблюдение. Представлено клиническое наблюдение пациента 7 лет с синдромом Лоеса – Дитца с генетически подтвержденным диагнозом.

Обсуждение. Приведен обзор литературы, рассмотрены вопросы диагностики и дифференциальной диагностики, а также клиническая картина синдрома. Основными симптомами синдрома Лоеса – Дитца являются аневризмы артерий (чаще всего корня аорты), извилистость артерий (преимущественно сосудов шеи), гипертелоризм и расщепленный или широкий язычок. Однако данные признаки не всегда присутствуют у всех пациентов с этим заболеванием.

Заключение. Генетическая верификация заболевания, а также мультидисциплинарный подход к лечению с обязательным динамическим наблюдением таких специалистов, как кардиолог, невролог, ортопед, педиатр, позволяют предупреждать развитие осложнений и увеличивать продолжительность жизни пациентов с синдромом Лоеса – Дитца.

Ключевые слова: синдром Лоеса – Дитца; аневризма и расслоение аорты; генерализованная извитость артерий; трансформирующий фактор роста β.

Loeys–Dietz syndrome is a rare autosomal dominant disease of the connective tissue, characterized by the cardiovascular system pathology (aneurysmal dilatation, dissection of the aorta and other medium and large arteries, and generalized tortuosity of the arteries with an aggressive nature of progression) combined with various abnormalities of the musculoskeletal system [1].

This disease was first described by the Belgian physician Bart L. Loeys and American physician Harry S. Dietz in 2005 [2, 3]. According to the authors, there are no specific clinical criteria for this syndrome, and the clinical diagnosis should be confirmed by a molecular genetic test with the detection of specific mutations [1].

If one of the parents has the Loeys–Dietz syndrome, the probability of having a child with this pathology is 50%. Approximately 25% of patients have close relatives with the same diagnosis, and the disease occurs *de novo* in 75% of cases [4].

Table 1

Types of Loeys–Dietz syndrome

Type	Chromosome	Gene
Type 1 Loeys–Dietz syndrome	9q22.33	*TGFBR1*
Type 2 Loeys–Dietz syndrome	3q24.1	*TGFBR2*
Type 3 Loeys–Dietz syndrome	15q22.33	*SMAD3*
Type 4 Loeys–Dietz syndrome	1q41	*TGFB2*
Type 5 Loeys–Dietz syndrome	14q24.3	*TGFB3*
Type 6 Loeys–Dietz syndrome	There is no data	*SMAD2*

Approximately three-quarters of patients with Loeys–Dietz syndrome have characteristic cranial and facial signs of the disease (cleft palate, hypertelorism, and/or craniosynostosis) [4]. Clinically, the syndrome usually manifests itself during the first year of life, including immediately after birth, but the first signs may also appear in adulthood [5–7]. There are reports of the detection of symptoms of this syndrome in the fetus [8–10].

The disease is characterized by an unfavorable prognosis. Data on the average life expectancy of patients with Loeys–Dietz syndrome vary from 26 to 37 years [2, 11]. A fatal outcome usually occurs because of dissection or rupture of the aortic aneurism, other large-caliber arteries, and intracranial hemorrhages [12].

Genetic causes of Loeys–Dietz syndrome are mutations in genes encoding the transforming growth factor β_1 and β_2 receptors (*TGFBR1* and *TGFBR2*, respectively) [1]. Subsequently, it was determined that mutations in the *SMAD3* gene, in the ligand genes of *TGFBR2* and *TGFB3* are also associated with phenotypic aspects determined by Loeys–Dietz syndrome [1, 13–17]. Thus, mutations in all of these five genes demonstrate the altered signal transmission of TGFB, which is clinically manifested by similar changes in the cardiovascular system, as well as craniofacial and skeletal abnormalities [2, 3, 13–16]. Meester et al. [18] reported the presence of type 6 Loeys–Dietz syndrome with a defect in the *SMAD2* gene without clarifying the clinical features (Table 1).

We did not find in the literature the descriptions of clinical signs characteristic of a particular type of the syndrome. To confirm and verify the diagnosis, it is necessary to conduct a molecular genetic study to identify specific mutations.

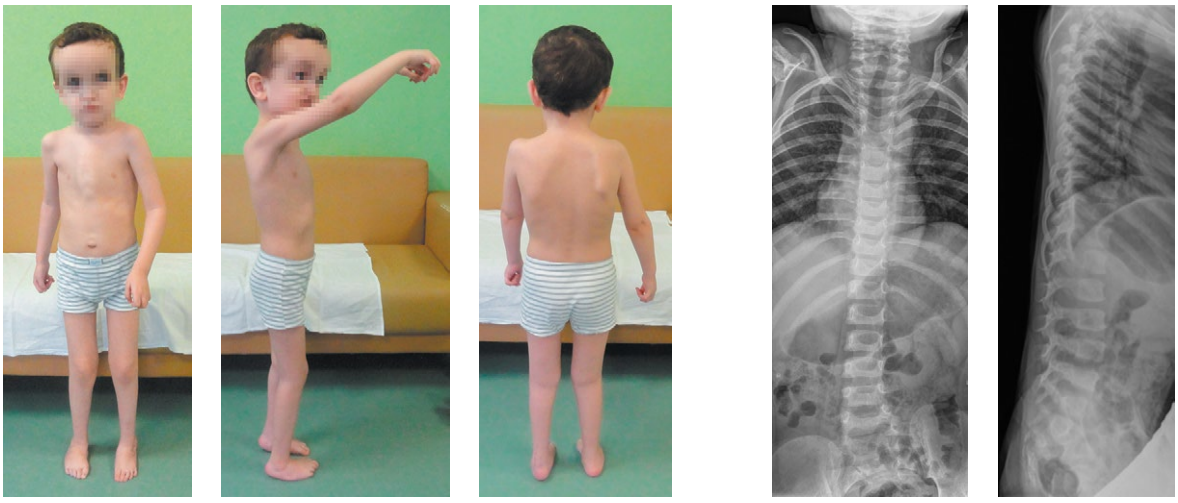
It is currently not possible to estimate reliably the prevalence of Loeys–Dietz syndrome in a population because of the lack of large-scale epidemiological studies.

Clinical case

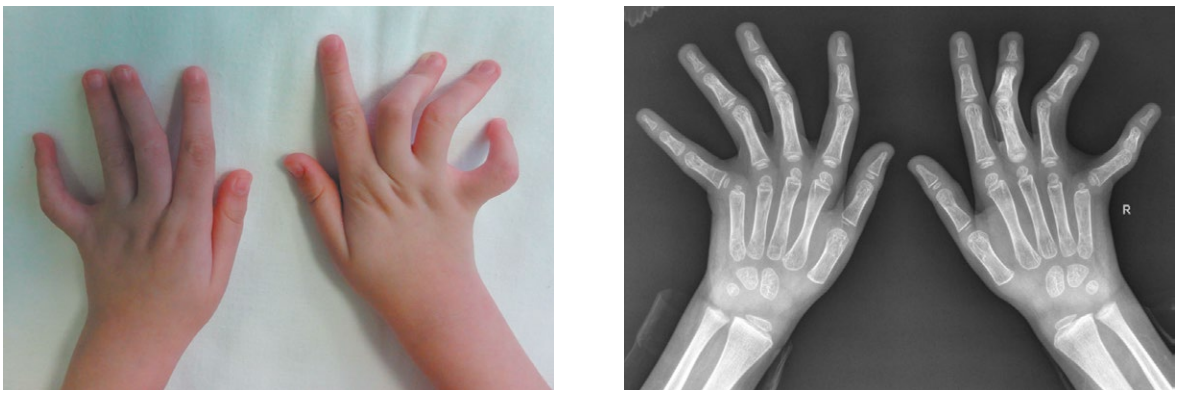
Our follow-up case involved a 7-year-old boy with malformations of the upper and lower extremities and pathology of the cardiovascular and nervous systems. The anamnesis reveals that the child was from the fifth pregnancy proceeding with toxicosis. The childbirth was third, operative, and in time. The hereditary history of the underlying disease was not burdened. In trimester I of pregnancy, the mother had an acute respiratory viral infection and also received antibacterial therapy against chlamydial infection. An ultrasound screening at 32–33 weeks of gestation revealed signs of congenital clubfoot in the fetus. The weight of the child at birth was 3500 g, and the body length was 54 cm. At the first clinical examination, congenital clubfoot, deformity of the hands, signs of craniofacial dimorphism, and hydrocephalus were found. Since the age of 2 months, clubfoot treatment was performed in one of the medical institutions in Russia, according to the Ponseti method. At the age of 2 years, the boy underwent surgery, including the posterior release of the ankle and subtalar joints, transposition of tendons of the anterior tibial muscle onto the sphenoid bone III on the left foot, and tenotomy of the tendons of the long flexors of toes I–V of the left foot and toes II and III of the right foot.

During a clinical orthopedic examination of the child upon admission, the following was established (Fig. 1). The physique was hyposthenic. He walked independently while limping on his left leg, slightly bending his legs at the knee joints, and rolling disorder and varus positioning of the feet. The skull was deformed, with scaphocephaly combined with right occipital plagiocephaly and pronounced frontal tubers. A high palate, micrognathia, retrogenia, short nasal dorsum, hypoplasia of the wings of the nose, hypertelorism, blue sclera, low location of auricles, and increased skin elasticity, narrow sparrow chest with a parasternal symmetrical impression of the ribs, and asymmetry of the shoulder girdle and the angles of the shoulder blades were noted. The axis of the spine deviated to the right in the thoracolumbar region. Asymmetry of paravertebral muscles. There was a right-sided thoracolumbar scoliosis of I degree (the scoliotic arch angle was 9°). There were signs of connective tissue dysplasia, including an excessive extension in the elbow and metacarpophalangeal knee joints. Extensor contractures in the radiocarpal joints were passively corrected. The first radii of the hands were in opposition. On the right hand, there were flexion contractures in the proximal interphalangeal joints of fingers III and IV at an angle of 145° and finger V at an angle of 90°, which were not corrected. On the left hand, there were flexion contractures in the proximal interphalangeal joints of the fingers II–V at an angle of 160°, which were partially corrected. There was ulnar deviation of finger V of both hands. The function of a two-sided grip with both hands was preserved. In the knee joints, the flexion and hyperextension were 30° and 25°, respectively. The valgus alignments in the knee joints were 20° in the right and 10° in the left. The inner torsion angles of the lower leg bones were 20° on the right and 10° on the left. The right foot had cavus deformity with the forefoot adduction and calcaneus varus. The left foot had a calcaneal deformity and a flattened longitudinal arch.

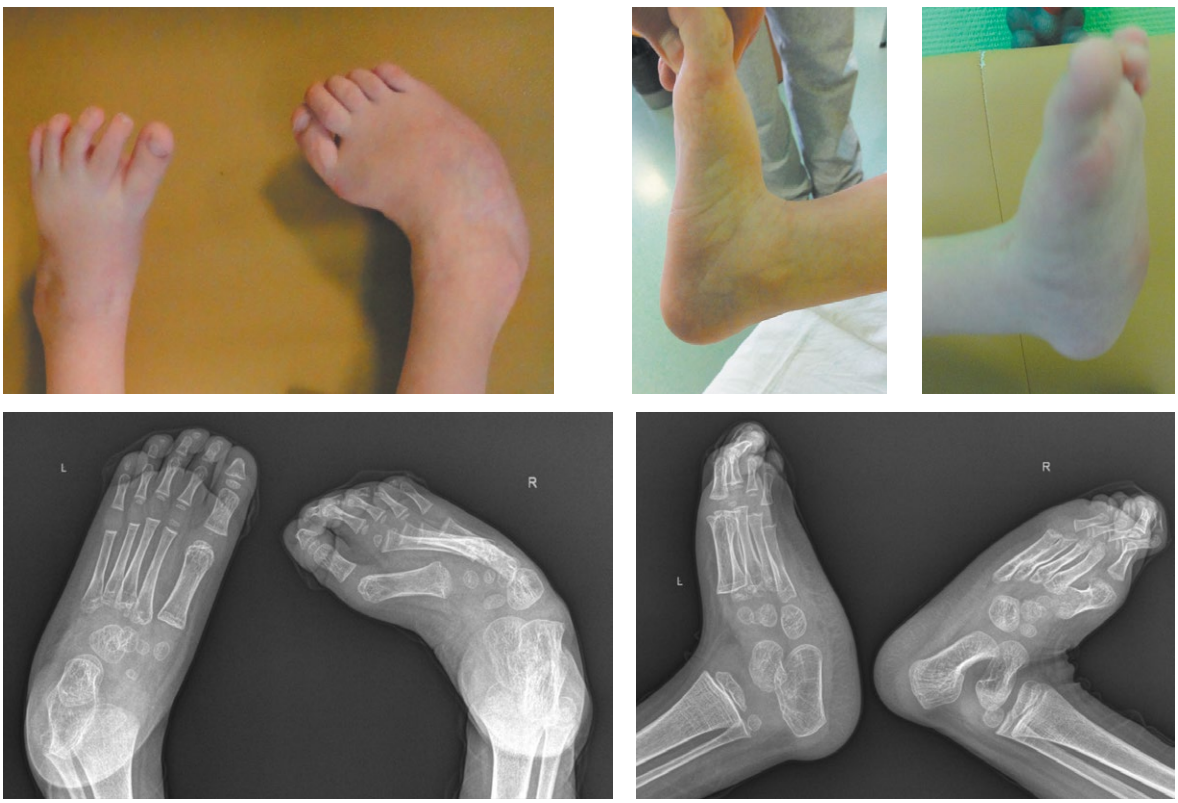
An X-ray examination of the hands and feet revealed the following. A moderate reduction in the size of the left hand bones, adduction of finger I ($S > D$), pronounced ulnar deviation in the metacarpophalangeal joints of finger V of both hands, and flexion contractures and ulnar deviation in the proximal interphalangeal joints of fingers III and IV of both hands. Multiplanar deformity of both feet was observed. In the right foot, the forefoot is adducted, with signs of supination, and the scaphoid bone is in the position of pronounced external dorsal decentration with deformity of the longitudinal arch with the caudal location of the apex, signs of the longitudinal arch excavation, and moderate osteoporosis. The left foot is adducted, with a longitudinal arch significantly flattened, pronounced dorsum-varus decentration of the scaphoid bone (at the boundary of the subluxation), moderate shortening of metatarsal bone I, and moderate osteoporosis.



a *b*



c



d

Patient A.: (*a*) Appearance of the patient; (*b*) radiographs of the spine; (*c*) appearance and radiographs of the hands; (*d*) appearance and radiographs of the feet

Radiography of the spine showed a sharp straightening of physiological curves in the sagittal plane and moderate lordosis at the Th_6–Th_9 level. Twisted pelvis to the right was seen. *Spina bifida posterior displastica* of the S_1–S_2 vertebrae without changing the size of the spinal canal and signs of instability at the L_5–S_1 level (displacement of the L_5 vertebral body anteriorly by up to 4 mm) were noted. The position of the sacrum was vertical.

Echocardiography with color Doppler examination revealed a minor dilation of the aortic root (up to 15 mm). The patient was consulted by a cardiologist. According to the conclusion, no pathology of the heart was detected, and there was a minor dilation of the aortic root, NK-0.

The boy was examined by a neurologist. A conclusion of residual encephalopathy, intraventricular hemorrhage convalescence, periventricular leukomalacia, combined communicating hydrocephalus, pseudobulbar dysarthria, and myopathic symptom complex in the genetic syndrome structure was made.

Examination by an ophthalmologist revealed hypertelorism, mild hypermetropia, and no abnormalities in the fundus.

To verify the disease, a molecular genetic examination was performed using the targeted DNA sequestration method using the panel "Marfan syndrome and Marfan-like syndromes." The study was conducted by the selective capture method of DNA regions belonging to the coding regions of genes with known clinical relevance, including *ACTA2*, *COL3A1*, *COL5A1*, *COL5A2*, *FBN1*, *FBN2*, *MYH11*, *SLC2A10*, *SMAD3*, *TGFB2*, *TGFBR1*, and *TGFBR2*. A previously undescribed heterozygous mutation in exon 6 of the *TGFBR2* gene (chr3:30715721G>C) was revealed, leading to the replacement of the amino acid at position 485 of the protein (p.Arg485Pro, NM_001024847.2). Heterozygous mutations in the *TGFBR2* gene have been described in patients with type 2 Loeys–Dietz syndrome (OMIM:610168). Subsequently, the child was consulted by a geneticist, and based on the examination results, type 2 Loeys–Dietz syndrome with an autosomal dominant type of inheritance was established.

Discussion

The main symptoms of Loeys–Dietz syndrome are as follows: aneurysms of the arteries (most often the aortic root), tortuosity of arteries (mainly neck vessels), hypertelorism, and split or wide uvula.

However, it should be remembered that these signs are not combined in all patients with this disease [19].

Pathology of the cardiovascular system with Loeys–Dietz syndrome

Patients with types 1 or 2 Loeys–Dietz syndrome with severe craniofacial dimorphism have an especially high risk of rupture of aneurysms at an early age and smaller sizes than patients with isolated vascular aneurysms or with other syndromes without pathological dilation of the arteries in the clinical presentation [2, 3]. In the literature, there are reports of diagnosed aortic dissection in patients aged 3 months and cerebral hemorrhage in patients under the age of 3 years [20, 21].

Patients with types 1 and 2 Loeys–Dietz syndrome are more likely to have congenital heart defects, such as a bicuspid aortic valve, an atrial septal defect, or an open arterial duct than the general population [4, 22]. Mild to severe prolapse and/or insufficiency of the mitral valve can be registered in all types of the syndrome [13, 22, 23]. Atrial fibrillation and left ventricular hypertrophy are most often recorded in patients with type 3 Loeys–Dietz syndrome (in 24% of cases), but they can also be noted in patients with other types of this syndrome [1]. Some authors report that left ventricular hypertrophy in patients with this syndrome is usually mild or moderate and occurs in the absence of aortic stenosis or arterial hypertension [21, 24]. Loeys et al. [3] and Eckman et al. [25] described the impaired systolic function of the left ventricle in patients with Loeys–Dietz syndrome.

According to Arslan-Kirchner et al. [26], all patients with Loeys–Dietz syndrome require an echocardiographic study at least once per year to monitor the condition of the aortic root, ascending aorta, and cardiac valves.

The decision to perform surgery on the aorta is usually based on the analysis of a set of data, including dynamic determination of the aorta anatomical parameters, valve function, noncardiac aspect severity, family history, and genotype information [3, 27].

Because of the active nature of the aortic aneurysm progression and the high risk of its rupture, the indication for surgical intervention on

the aorta is the size of its root, which is equal to 4.0 cm in adults [1]. In children, surgery is postponed until the diameter of the aortic root increases to 2.0–2.2 cm. However, if the aorta dilates slowly, the surgery is performed in children when the aortic root size approaches a threshold of 4.0 cm in some cases [1]. A rapid increase in the size of the aortic root diameter (>0.5 cm per year) should also be an indication for early surgical correction.

Open recovery of descending and thoracoabdominal aneurysms is optimal because endovascular recovery can lead to late complications due to continued dilatation of the zone or continuous perfusion of the false lumen [20, 26]. Stenting can be reasonable for a descending rupture of the thoracic aorta or relieving hyperperfusion syndromes, such as recurrent hypertension or irregular renal artery perfusion secondary to acute dissection. Cases of complete phased aortic replacement in patients with Loeys–Dietz syndrome have been described [28]. Postoperative echocardiography is recommended to perform with an interval of 3 to 6 months within a year after surgery and then every 6 months [29].

In addition to case follow-up and surgical correction of the aorta and affected arteries, antihypertensive drugs must be used, stimulating drug or vasoconstrictor intake must be avoided, and physical activity must also be limited. Sport is prohibited to patients with this pathology [1]. In the case of diagnosis of Loeys–Dietz syndrome in children under 1 year of age, the early therapy with angiotensin-converting enzyme inhibitors or beta-blockers is indicated to control the rate of aortic dilatation progression [1].

The pathological tortuosity of the arteries can be generalized but is most often noted in the vessels of the neck and head for all types of Loeys–Dietz syndrome [3, 4, 13]. For diagnosing the condition of the arteries, it is advisable to conduct magnetic resonance or computed angiography with the construction of three-dimensional images of the vessels of the head, neck, chest, abdomen, and pelvis. This method is preferred since there is no radiation exposure during magnetic resonance imaging. Complete visualization of blood vessels in children must be performed during initial diagnostics and then with an interval of Approximately 2 years in the absence of aneurysms or dissections [2, 3].

Orthopedic pathology in Loeys–Dietz syndrome

Skeletal abnormalities in Loeys–Dietz syndrome include deformities of the chest (more often cobbler's chest and less often sparrow chest), spine (scoliosis), extremities (congenital clubfoot, arachnodactyly, camptodactyly, metacarpophalangeal joint dislocations, forearm bone dislocations, and joint extensor contractures), and skull. Cases of joint hypermobility, multiple joint subluxations, and congenital hip dislocations in patients with Loeys–Dietz syndrome have been reported [3]. In the first year of life, these children usually have reduced muscle tone. It is important to remember that when performing exercises to stimulate muscle tone, techniques with hyperextension must be excluded [5].

Such deformities of the feet as clubfoot or platypodia can be registered. Congenital clubfoot in such patients is recovered well using conservative therapy if the deformity is not severely pronounced. Surgery is generally not recommended, as it usually leads to excessive correction (valgus of the hindfoot) [30]. Surgical intervention with platypodia is also not indicated, except in cases of severe pain that limits walking [1].

Pathology of the cervical spine is a characteristic sign of types 1 and 2 Loeys–Dietz syndrome and occurs in 51% of cases [3, 31]. Defects of the cervical vertebral arches are detected most often, as well as subluxations of the C_1 and C_2 vertebrae, which result in the cervical spine instability [32].

Progressive scoliotic and kyphotic deformities, as well as spondylolisthesis, most often develop out of the spinal pathology. In this case, follow-up is required at least once a year until the skeleton matures [3, 29].

Osteoarthritis and osteoarthrosis represent a characteristic feature of patients with type 3 Loeys–Dietz syndrome. Arthrosis usually affects the knee, hip joints, small hand and feet joints, and spinal joints already in adolescence, which requires conservative treatment [13, 21].

The literature contains reports of low bone mineral density and frequent fractures in young patients with Loeys–Dietz syndrome [2, 30, 31].

Other clinical manifestations of Loeys–Dietz syndrome

Patients with Loeys–Dietz syndrome often show signs of craniofacial dimorphism. It is believed that hypertelorism and abnormalities of the palatine

uvula (bilobed, wide, or long uvula) are characteristic signs; however, many patients with this syndrome do not have these symptoms [1].

Cleft palate and craniosynostosis are registered in patients with types 1 and 2 of the syndrome. Most often, premature closure of the sagittal suture with the formation of dolichocephaly is noted, but other sutures of the skull can also be involved [1].

Other craniofacial features of the Loeys–Dietz syndrome are represented by micrognathism or retrognathism, cheekbone flattening, and a high and wide forehead with a high front line of hair growth [18].

Patients with Loeys–Dietz syndrome are at a high risk of developing allergic reactions, including bronchial asthma, food allergies, allergic rhinitis, atopic dermatitis, and eczema [33]. According to MacCarrick et al. [1], food allergies are noted in 31% of cases (compared with 6–8% prevalence in the general population) in patients with this syndrome. The severity of allergic reactions is different. Antihistamines are recommended for the treatment of skin or milder allergic reactions. The use of adrenomimetics and sympathomimetics in patients with this syndrome is limited because of their pressor effect on blood vessels, and therefore, their use is justified only in cases of severe allergic reactions [1].

In patients with type 2 Loeys–Dietz syndrome, the skin is velvet, thin, and translucent [3]; therefore, wound healing usually takes a long time, and scars are usually atrophic [25].

MacCarrick et al. [1] noted the more frequent prevalence of inguinal and umbilical hernias in pediatric patients with Loeys–Dietz syndrome than in the population as a whole.

The literature provides reports of spontaneous rupture of the intestines and spleen in patients with this syndrome [18].

Mental retardation and learning disability are registered rarely in patients with this syndrome and are probably associated with craniosynostosis or hydrocephalus. There are no data on the mental dysfunctions in patients with type 3 Loeys–Dietz syndrome [1].

Arnold–Chiari malformation with this syndrome is rare. Hydrocephalus may occur, but it is usually not associated with Chiari defect. Dural ectasia is now increasingly frequently found in patients with Loeys–Dietz syndrome, which is due to the widespread use of modern methods of radiation diagnostics [29].

Ophthalmological problems in Loeys–Dietz syndrome include heterotropia (usually exotropia), amblyopia, and cataracts. Patients with this syndrome often have blue sclera. Myopia is rare [3].

Loeys–Dietz syndrome is associated with a high prevalence of eosinophil-associated gastrointestinal disorders [32]. According to MacCarrick et al. [1], patients with this pathology have eosinophilic esophagitis, eosinophilic gastritis, and/or eosinophilic colitis.

Pediatric patients with Loeys–Dietz syndrome often gain weight poorly [32].

Table 2 presents the main symptoms of Loeys–Dietz syndrome [19].

When treating patients with this syndrome, it is necessary to bear in mind the emergence of hazardous complications, such as death due to rupture of the aortic aneurysm, stroke due to rupture of an aneurysm of the neck arteries, spontaneous pneumothorax, hemoptysis, retinal detachment, and rupture of hollow organs (intestines and uterus) and spleen [19].

Differential diagnostics of Loeys–Dietz syndrome should be performed with diseases, such as Marfan syndrome, Beals syndrome, and Ehlers–Danlos (EDS) syndrome.

Marfan syndrome has an autosomal dominant inheritance type and is caused by mutations of the *FBN1* gene. The key primary manifestations of Marfan syndrome are dilatation of the aortic root and ectopia lentis. Compared with Marfan syndrome, patients with Loeys–Dietz syndrome have a malignant and progressive course of aortic aneurysm and tortuosity of the arterial bed vessels; aortic aneurysms tend to dissect and rupture with a smaller diameter at a younger age as well; aneurysms in Loeys–Dietz syndrome are not limited to the root or ascending aorta and often affect other large vessels and cerebral vessels [18]. Congenital heart defects with Marfan syndrome are much less common compared with Loeys–Dietz syndrome [34]. Joint hypermobility is noted in most patients with Marfan syndrome, whereas the presence of this symptom in Loeys–Dietz syndrome depends on the defect of a particular gene. Patients with type 3 Loeys–Dietz syndrome are most often characterized by joint hypermobility with degenerative changes in them [21]. Arachnodactyly is more pronounced in

Table 2

Main symptoms of Loeys–Dietz syndrome

Localization	Symptoms
Cardiovascular system	Congenital heart defects: open arterial duct, atrial or interventricular septal defect, and bicuspid aortic valve
Organ of vision	Myopia (myopia) Pathology of the eye muscles Retinal detachment
Craniofacial region	Flat cheekbones Slight slope down to the eyes Craniosynostosis Cleft palate Blue sclera Micrognathia and/or retrognathia
Musculoskeletal system	Long fingers and toes Finger contractures Clubfoot Scoliosis Instability of the cervical spine Joint hypermobility Cobbler's chest/sparrowy chest Osteoarthritis Normal height
Skin	Translucent Soft or velvet Easily injured Atrophic scars Hernia of the anterior abdominal wall
Other	Food or environmental allergies Gastrointestinal inflammatory diseases Hollow organs (intestines, uterus) and spleen tend to rupture

patients with Marfan syndrome. Joint contractures in patients with Loeys–Dietz syndrome are determined more often. Scoliotic spinal deformities, platypodia, chest deformities, and dural ectasia are common skeletal features of Loeys–Dietz syndrome and Marfan syndrome. There are no data on the ectopia of the lens in patients with Loeys–Dietz syndrome, whereas this is the main distinguishing sign in Marfan syndrome [18]. Myopia with Marfan syndrome is registered much more often than with Loeys–Dietz syndrome [1]. Blue sclera is noted in patients with Loeys–Dietz syndrome and is usually not registered in patients with Marfan syndrome [3]. In some patients with Loeys–Dietz syndrome without craniofacial abnormalities, skin signs (thin, velvet, and translucent skin) can be a noticeable distinguishing feature in comparison with patients with Marfan syndrome [4, 13]. Hypertelorism and abnormalities of the palatine uvula in patients with Marfan syndrome have not been described [18].

EDS is a group of connective tissue diseases that are clinically and genetically heterogeneous. Moreover, all subtypes are characterized by abnormalities of the skin, ligaments and joints, blood vessels, internal organs, and skeletal pathologies (cobbler's chest, platypodia, and kyphoscoliosis) [18]. Joint hypermobility, skin hypersensitivity, and soft tissue fragility are the most common manifestations. Up to a quarter of patients with EDS suffer from aortic aneurysm [35]. EDS is caused by mutations in genes encoding collagen fibrils or proteins involved in the processing of these collagens [18]. When healing, "cigarette" or keloid scars are formed in patients with EDS, [36] in contrast to atrophic scars in Loeys–Dietz syndrome.

Beals syndrome is a rare autosomal dominant disease of the connective tissue, characterized by arachnodactyly, congenital joint contractures, scoliotic spinal deformity, chest deformity, platypodia, and an altered shape of the auricles ("crumpled ear"). The disease is caused by a mutation of the *FBN2* gene [36]. Beals syndrome, in contrast to Loeys–Dietz syndrome, is considered a benign disease in which the features of the cardiovascular system are, in most cases, limited to mitral valve prolapse. However, approximately

15–20% of patients with Beals syndrome have aortic aneurysm; other congenital heart defects are also registered. In contrast to the Loeys–Dietz syndrome, congenital joint contractures tend to involute with age in Beals syndrome [36].

Valenzuela et al. recommended differential diagnostics of Loeys–Dietz syndrome with congenital multiple arthrogryposis. However, with arthrogryposis, there are no abnormalities in the cardiovascular system, typical for this syndrome [37].

In the case of suspected Loeys–Dietz syndrome, the patient must complete the entire range of additional examinations, including the following:

- an ultrasound examination of the heart followed by a consultation with a cardiologist;
- computed tomography angiography or magnetic resonance imaging to assess the arterial bed of the head, neck, chest, abdominal cavity, and pelvis;
- consultation with a neurologist, ophthalmologist, and a genetic scientist; and
- molecular genetic examinations of the patients and their parents to identify mutations in the *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, and *TGFB3* genes.

Conclusion

Thus, Loeys–Dietz syndrome is a disease in which case follow-up of the pediatric patient by many specialists is required, especially a cardiologist, neurologist, orthopedist, and pediatrician. Early diagnostics and competent management prevent the development of complications and increase the life expectancy of patients with this syndrome.

The study of a relatively recently discovered genetic syndrome with a polymorphism of clinical manifestations should be continued, as well as the publication of new clinical cases.

Additional information

Source of funding. The authors declare to have no financial support for the study.

Conflict of interests. The authors declare no obvious or potential conflicts of interest related to the publication of this article.

Ethical statement. The authors obtained the written consent of the patient's legal representatives to analyze and publish the medical data.

Author contributions

O.E. Agranovich performed surgical treatment of the patient, reviewed the literature, collected and analyzed literature, wrote the text, and edited the article.

S.Yu. Semenov performed a literature review, collected and analyzed the literature sources, and prepared and wrote the text of the article.

E.F. Mikiashvili performed supervision and surgical treatment of the patient, collected and analyzed the literature sources, and prepared and wrote the text of the article.

S.V. Sarantseva performed the literature review, collected and analyzed the literature sources, wrote the text, and edited the article.

All authors made a significant contribution to the research and preparation of the article, read and approved the final version before its publication.

References

1. MacCarrick G, Black JH, 3rd, Bowdin S, et al. Loeys-Dietz syndrome: a primer for diagnosis and management. *Genet Med*. 2014;16(8):576-587. https://doi.org/10.1038/gim.2014.11.
2. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. *N Engl J Med*. 2006;355(8):788-798. https://doi.org/10.1056/NEJMoa055695.
3. Loeys BL, Chen J, Neptune ER, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. *Nat Genet*. 2005;37(3):275-281. https://doi.org/10.1038/ng1511.
4. Van Hemelrijk C, Renard M, Loeys B. The Loeys-Dietz syndrome: an update for the clinician. *Curr Opin Cardiol*. 2010;25(6):546-551. https://doi.org/10.1097/HCO.0b013e32833f0220.
5. Yetman AT, Beroukhim RS, Ivy DD, Manchester D. Importance of the clinical recognition of Loeys-Dietz syndrome in the neonatal period. *Pediatrics*. 2007;119(5):e1199-1202. https://doi.org/10.1542/peds.2006-2886.
6. Muramatsu Y, Kosho T, Magota M, et al. Progressive aortic root and pulmonary artery aneurysms in a neonate with Loeys-Dietz syndrome type 1B. *Am J Med Genet A*. 2010;152A(2):417-421. https://doi.org/10.1002/ajmg.a.33263.
7. Chung BH, Bradley T, Grosse-Wortmann L, et al. Hand and fibrillin-1 deposition abnormalities in Loeys-Dietz syndrome — expanding the clinical spectrum. *Am J Med Genet A*. 2014;164A(2):461-466. https://doi.org/10.1002/ajmg.a.36246.
8. Viassolo V, Lituania M, Marasini M, et al. Fetal aortic root dilation: a prenatal feature of the Loeys-Dietz syn-

drome. *Prenat Diagn*. 2006;26(11):1081-1083. https://doi.org/10.1002/pd.1565.

9. Kawazu Y, Inamura N, Kayatani F, et al. Prenatal complex congenital heart disease with Loeys-Dietz syndrome. *Cardiol Young*. 2012;22(1):116-119. https://doi.org/10.1017/S1047951111001028.

10. Ozawa H, Kawata H, Iwai S, et al. Pulmonary artery rupture after bilateral pulmonary artery banding in a neonate with Loeys-Dietz syndrome and an interrupted aortic arch complex: report of a case. *Surg Today*. 2015;45(4):495-497. https://doi.org/10.1007/s00595-014-0910-8.

11. Woolnough R, Dhawan A, Dow K, Walia JS. Are patients with Loeys-Dietz syndrome misdiagnosed with beals syndrome? *Pediatrics*. 2017;139(3). https://doi.org/10.1542/peds.2016-1281.

12. Журавлева Л.В., Романенко А.Р. Поражение сердечно-сосудистой системы при наследственных заболеваниях соединительной ткани // Східноєвропейський журнал внутрішньої та сімейної медицини. – 2016. – № 1. – С. 104–110. [Zhuravleva LV, Romanenko AR. Involvement of cardiovascular system in hereditary disorders of connective tissue. *Skhidnoєvropeĭs'kiĭ zhurnal vnutrishn'oï ta simeĭnoï meditsini*. 2016;(1):104-110. (In Russ.)]

13. van de Laar IM, Oldenburg RA, Pals G, et al. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. *Nat Genet*. 2011;43(2):121-126. https://doi.org/10.1038/ng.744.

14. Regalado ES, Guo DC, Villamizar C, et al. Exome sequencing identifies SMAD3 mutations as a cause of familial thoracic aortic aneurysm and dissection with intracranial and other arterial aneurysms. *Circ Res*. 2011;109(6):680-686. https://doi.org/10.1161/CIRCRESAHA.111.248161.

15. Lindsay ME, Schepers D, Bolar NA, et al. Loss-of-function mutations in TGFB2 cause a syndromic presentation of thoracic aortic aneurysm. *Nat Genet*. 2012;44(8):922-927. https://doi.org/10.1038/ng.2349.

16. Boileau C, Guo DC, Hanna N, et al. TGFB2 mutations cause familial thoracic aortic aneurysms and dissections associated with mild systemic features of Marfan syndrome. *Nat Genet*. 2012;44(8):916-921. https://doi.org/10.1038/ng.2348.

17. Bertoli-Avella AM, Gillis E, Morisaki H, et al. Mutations in a TGF-beta ligand, TGFB3, cause syndromic aortic aneurysms and dissections. *J Am Coll Cardiol*. 2015;65(13):1324-1336. https://doi.org/10.1016/j.jacc.2015.01.040.

18. Meester JAN, Verstraeten A, Schepers D, et al. Differences in manifestations of Marfan syndrome, Ehlers-Danlos syndrome, and Loeys-Dietz syndrome. *Ann Cardiothorac Surg*. 2017;6(6):582-594. https://doi.org/10.21037/acs.2017.11.03.

19. loeysdietz.org [Internet]. Loeys-Dietz Syndrome Foundation [cited 07 feb 2020]. Available from: https://www.loeysdietz.org/en/medical-information.

20. Malhotra A, Westesson PL. Loeys-Dietz syndrome. *Pediatr Radiol*. 2009;39(9):1015. https://doi.org/10.1007/s00247-009-1252-3.

21. Williams JA, Loeys BL, Nwakanma LU, et al. Early surgical experience with Loeys-Dietz: a new syndrome of aggressive thoracic aortic aneurysm disease. *Ann Thorac Surg*. 2007;83(2):S757-763. https://doi.org/10.1016/j.athoracsur.2006.10.091.

22. van de Laar IM, van der Linde D, Oei EH, et al. Phenotypic spectrum of the SMAD3-related aneurysms-osteoarthritis syndrome. *J Med Genet*. 2012;49(1):47-57. https://doi.org/10.1136/jmedgenet-2011-100382.

23. Renard M, Callewaert B, Malfait F, et al. Thoracic aortic-aneurysm and dissection in association with significant mitral valve disease caused by mutations in TGFB2. *Int J Cardiol*. 2013;165(3):584-587. https://doi.org/10.1016/j.ijcard.2012.09.029.

24. van der Linde D, van de Laar IM, Bertoli-Avella AM, et al. Aggressive cardiovascular phenotype of aneurysms-osteoarthritis syndrome caused by pathogenic SMAD3 variants. *J Am Coll Cardiol*. 2012;60(5):397-403. https://doi.org/10.1016/j.jacc.2011.12.052.

25. Eckman PM, Hsich E, Rodriguez ER, et al. Impaired systolic function in Loeys-Dietz syndrome: a novel cardiomyopathy? *Circ Heart Fail*. 2009;2(6):707-708. https://doi.org/10.1161/CIRCHEARTFAILURE.109.888636.

26. Arslan-Kirchner M, Epplen JT, Faivre L, et al. Clinical utility gene card for: Loeys-Dietz syndrome (TGFBR1/2) and related phenotypes. *Eur J Hum Genet*. 2011;19(10). https://doi.org/10.1038/ejhg.2011.68.

27. Edelman JJ, Ramponi F, Bannon PG, Jeremy R. Familial aortic aneurysm and dissection due to transforming growth factor-beta receptor 2 mutation. *Interact Cardiovasc Thorac Surg*. 2011;12(5):863-865. https://doi.org/10.1510/icvts.2010.258681.

28. Williams JB, McCann RL, Hughes GC. Total aortic replacement in Loeys-Dietz syndrome. *J Card Surg*. 2011;26(3):304-308. https://doi.org/10.1111/j.1540-8191.2011.01224.x.

29. Cleuziou J, Eichinger WB, Schreiber C, Lange R. Aortic root replacement with re-implantation technique in an infant with Loeys-Dietz syndrome and a bicuspid aortic valve. *Pediatr Cardiol*. 2010;31(1):117-119. https://doi.org/10.1007/s00246-009-9541-z.

30. Erkula G, Sponseller PD, Paulsen LC, et al. Musculoskeletal findings of Loeys-Dietz syndrome. *J Bone Joint Surg Am*. 2010;92(9):1876-1883. https://doi.org/10.2106/JBJS.I.01140.

31. Ben Amor IM, Edouard T, Glorieux FH, et al. Low bone mass and high material bone density in two patients with Loeys-Dietz syndrome caused by transforming growth factor beta receptor 2 mutations. *J Bone Miner Res*. 2012;27(3):713-718. https://doi.org/10.1002/jbmr.1470.

32. Kirmani S, Tebben PJ, Lteif AN, et al. Germline TGF-beta receptor mutations and skeletal fragility: a report on two patients with Loeys-Dietz syndrome.

Am J Med Genet A. 2010;152A(4):1016-1019. https://doi.org/10.1002/ajmg.a.33356.

33. Frischmeyer-Guerrerio PA, Guerrerio AL, Oswald G, et al. TGFbeta receptor mutations impose a strong predisposition for human allergic disease. *Sci Transl Med*. 2013;5(195):195ra194. https://doi.org/10.1126/scitranslmed.3006448.

34. Attias D, Mansencal N, Auvert B, et al. Prevalence, characteristics, and outcomes of patients presenting with cardiogenic unilateral pulmonary edema. *Circulation*. 2010;122(11):1109-1115. https://doi.org/10.1161/CIRCULATIONAHA.109.934950.

35. Verstraeten A, Alaerts M, Van Laer L, Loeys B. Marfan syndrome and related disorders: 25 years of gene discovery. *Hum Mutat*. 2016;37(6):524-531. https://doi.org/10.1002/humu.22977.

36. Семячкина А.Н., Близнец Е.А., Воинова В.Ю., и др. Синдром Билса (врожденная контрактурная арахнодактилия) у детей: клиническая симптоматика, диагностика, лечение и профилактика // Российский вестник перинатологии и педиатрии. – 2016. – Т. 61. – № 5. – С. 47–51. [Semyachkina AN, Bliznets EA, Voinova V., et al. Beals syndrome (congenital contractural arachnodactyly) in children: Clinical symptoms, diagnosis, treatment, and prevention. *Rossiĭskiĭ vestnik perinatologii i pediatrii*. 2016;61(5):47-51. (In Russ.)]. doi.org/10.21508/1027-4065-2016-61-5-47-51.

37. Valenzuela I, Fernandez-Alvarez P, Munell F, et al. Arthrogryposis as neonatal presentation of Loeys-Dietz syndrome due to a novel TGFBR2 mutation. *Eur J Med Genet*. 2017;60(6):303-307. https://doi.org/10.1016/j.ejmg.2017.03.010.

Information about the authors

Olga E. Agranovich — MD, PhD, D.Sc., Head of the Department of Arthrogryposis, H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery, Saint Petersburg, Russia. https://orcid.org/0000-0002-6655-4108. E-mail: olga_agranovich@yahoo.com.

Sergei Yu. Semenov — MD, orthopedic and trauma surgeon, pediatric surgeon, State Children's City Hospital No. 22, Saint Petersburg. https://orcid.org/0000-0002-7743-2050. E-mail: sergey2810@yandex.ru.

Ольга Евгеньевна Агранович — д-р мед. наук, руководитель отделения артрогрипоза, ФГБУ «НМИЦ детской травматологии и ортопедии имени Г.И. Турнера» Минздрава России, Санкт-Петербург. https://orcid.org/0000-0002-6655-4108. E-mail: olga_agranovich@yahoo.com.

Сергей Юрьевич Семенов — врач — травматолог-ортопед, детский хирург, ГБУЗ «Детская городская больница № 22», Санкт-Петербург. https://orcid.org/0000-0002-7743-2050. E-mail: sergey2810@yandex.ru.

Eugeniya F. Mikiashvili — MD, orthopedic and trauma surgeon of the Department of Arthrogryposis, H. Turner National Medical Research Center for Children's Orthopedics and Trauma Surgery, Saint Petersburg, Russia. https://orcid.org/0000-0003-1286-3594. E-mail: mikiashviliy@bk.ru.

Svetlana V. Sarantseva — PhD, D.Sc., Head of Laboratory of Experimental and Applied Genetics, Deputy Director for Science, Petersburg Nuclear Physics Institute named by B.P. Konstantinov of NRC Kurchatov Institute, Leningrad Region, Russia. https://orcid.org/0000-0002-3943-7504. E-mail: sarantseva_sv@pnpi.nrcki.ru.

Евгения Федоровна Микиашвили — врач — травматолог-ортопед отделения артрогрипоза, ФГБУ «НМИЦ детской травматологии и ортопедии имени Г.И. Турнера» Минздрава России, Санкт-Петербург. https://orcid.org/0000-0003-1286-3594. E-mail: mikiashviliy@bk.ru.

Светлана Владимировна Саранцева — д-р биол. наук, заведующая лабораторией экспериментальной и прикладной генетики, заместитель директора по научной работе, ФГБУ «Петербургский институт ядерной физики им. Б.П. Константинова» НИЦ «Курчатовский институт», Санкт-Петербург. https://orcid.org/0000-0002-3943-7504. E-mail: sarantseva_sv@pnpi.nrcki.ru.