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COMBINATION OF ARRYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY WITH LOEYS-DIETZ SYNDROME: CASE REPORT

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Arrhythmogenic right ventricular dysplasia is a hereditary cardiomyopathy - a common cause of sudden cardiac death in children and young adults. Loeys-Dietz syndrome is an ultra-rare connective tissue disorder characterized by aneurysms of the aorta and other large arteries, arterial tortuosity, and joint hypermobility and is associated with pathogenic variants in genes encoding protein components TGF-β pathway. We present a rare case of a two-abovementioned genetic disorders combination in a proband with a complex and rapidly progressive cardiovascular syndrome.

Key words: arrhythmogenic right ventricular cardiomyopathy; Loeys-Dietz syndrome; connective tissue disorders; heritable cardiovascular disorders; children

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Arrhythmogenic right ventricular cardiomyopathy (ARVC), an inherited disease characterized by predominant involvement of the right ventricle (RV), is a prevalent cause of sudden cardiac death (SCD) in children and young adults. Often it is the SCD that is the first clinical manifestation of the disease. The incidence of ARVC is estimated to be 1 in 2000-5000 people, with the disease being twice as common and more severe in men [1]. ARVC usually manifests between the ages of 30-40 years, very rarely in children under the age of 10 years [2].

In ARVC, myocardial regions are replaced by fibro-fatty tissue, leading to the emergence of life-threatening cardiac rhythm disorders, accompanied by the appearance of hypokinetic zones. In 50% of cases of ARVC, the initial clinical presentation is often marked by the onset of fatal ventricular tachycardia and SCD [3]. Presumably, a significant role in the progressive myocardial degeneration is played by the process of apoptosis, as well as impaired formation of intercellular contacts [4].

There are 4 stages in the course of ARVC: clinically unidentifiable (myocardial structural abnormalities are minimal or absent, there are no clinical manifestations); arrhythmic (cardiac rhythm disturbances increase); RV heart failure (progressive replacement of cardiomyocytes by fibrous-fatty tissue is accompanied by impaired myocardial contractility) and the stage of biventricular heart failure (lesion of the interventricular septum, formation of aneurysms, atrial fibrillation). The final stage of ARVC is clinically akin to severe dilated cardiomyopathy (DCMP); hence, differential diagnosis with DCMP becomes imperative when diagnosing advanced stages of ARVC [5].

Typically, the development of ARVC is associated with pathogenic variants in one of eight genes - *PKP2,*

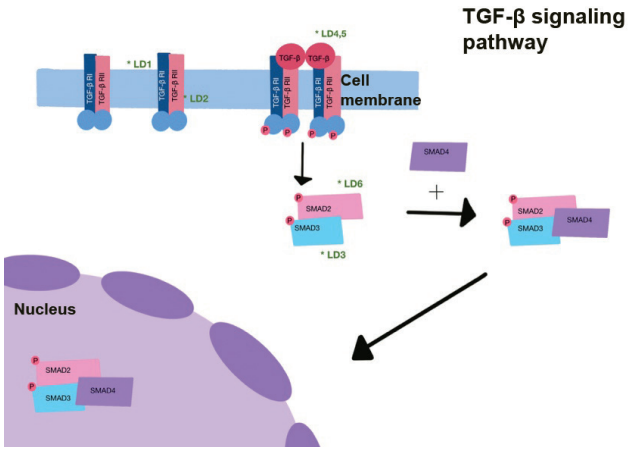

Fig. 1. TGF-β signaling pathway. Interaction of ligand (TGF-β) with the receptor proteins TGFBR1 and TGFBR2 leads to phosphorylation of SMAD family proteins. These proteins form a complex that penetrates into the nucleus where it regulates the expression of target genes of the TGF-β signaling pathway. Types of Lois-Dietz syndrome associated with pathogenic variants in genes encoding proteins of this signaling pathway are indicated in green.

DSP, DSG2, DSC2, JUP, TMEM43, DES, and *PLN* [6], most commonly, with dysfunction of desmosomal protein genes, particularly the *PKP2* gene, pathogenic variants in which are responsible for about half of all cases of ARVC [7]. The *PKP2* gene (OMIM: 602861) encodes plakophillin-2, which is a stabilizing part of the connection between the cytoskeleton and cadherins on muscle cell membranes. Structural abnormalities of this protein lead to dissociation of desmoplakin and accumulation of abnormal protein complexes in the cytoplasm and, subsequently, to impaired myocardial formation. Disruption of *PKP2* expression also leads to decreased sodium current and slower signal conduction in cardiomyocytes, which contributes to the development of arrhythmias [8]. Pathogenic variants in the *PKP2* gene are characterized by incomplete penetrance [9]. Other genes associated with the development of ARVC include the *TGFB3* gene, which encodes the TGF-β3 protein, a ligand of the TGF-β signaling pathway. Variants in the nontranslated region of this gene were found in nine relatives from one family with ARVC and 40 other healthy members of that family. The findings indicated that *TGFB3* overexpression leads to the development of ARVC, but the specific molecular mechanism underlying this dysregulation of expression has not been determined. [10]

Lois-Dietz syndrome (LDS) is a connective tissue disorder that was first described in 2005 by B.L. Lois, G.S. Dietz et al. The main clinical manifestations noted were: aneurysm of the aorta and other large arteries, pathological tortuosity of the arteries, joint hypermobility, cleft palate, bifurcation of the palatine uvula and hypertelorism of the eyes. At the time of description, pathogenic variants in the *TGFBR1* and *TGFBR2* genes encoding receptors for transforming growth factor β (TGF-β) have been associated with LDS [11].

Currently, 6 different types of LDS are known, each associated with pathogenic variants in genes whose protein products participate in the TGF-β signaling pathway (Fig. 1). TGF-β signaling pathway is named after the TGF-β protein and is essential for the regulation of cell proliferation and differentiation both in embryogenesis and postnatal period [12].

The third type of LDS (OMIM: 613795), also known as aneurysm-osteoarthritis syndrome (hereafter referred to as LDS3), is associated with pathogenic variants in the *SMAD3* gene (OMIM: 603109) encoding the protein of the same name [13]. The SMAD3 (Mothers against decapentaplegic homolog 3) protein is a member of the SMAD family and is a messenger protein in the TGF-β signaling pathway [14]. Pathogenic variants in the *SMAD3*gene lead to dysregulation of TGF-β signaling pathway in aortic tissue, which is the cause of the main clinical features of the disease, such as aortic aneurysm, aortic dissection, aortic valve insufficiency, mitral valve prolapse with regurgitation, and others. Dysregulation of the TGF-β signaling pathway is also associated with another, better known connective tissue disease, Marfan syndrome, which is characterized by similar abnormalities in cardiovascular tissues. Also, due to the presence of chest deformity, scoliosis and joint hypermobility, increased skin elasticity, tendency to the occurrence of striae and scars, frequent formation of hematomas, LDS3 has clinical similarities with another connective tissue disease - Ehlers-Danlo syndrome, primarily - with the vascular type. Therefore, a differential diagnosis with the aforementioned connective tissue diseases is recommended when making a clinical diagnosis of LDS3.

The LDS3 phenotype differs from other types of the syndrome in the early onset of osteoarthritis affecting mainly the joints of the lower extremities, as well as in the later manifestation [15]. Other clinical manifestations include dolichostenomelia, intervertebral disc degeneration, spondylolisthesis and spondylosis, atrial fibrillation, left ventricular (LV) hypertrophy, umbilical and inguinal hernias; prolapses of the rectum, uterus, and bladder; malocclusion, high palate, and arachnodactyly.

Clinical case

Proband, a girl, first pregnancy (Fig. 2). She was born at gestational age of 41 weeks, with a weight of 4500 g and body length of 59 cm. Early psychomotor development within normal limits. At the age of 5 years: after a respiratory infection with prolonged hyperthermia, heart murmurs, mitral valve prolapse, and dyspnea on physical exertion were detected for the first time by auscultation. No information on clinical findings during the proband's life from age 5 to 11 years was retained. Echocardiography performed for the first time at the age of 11 years revealed dilatation of the left atrial (LA) cavity. According to Holter monitoring (HM), there were tachycardia throughout the day and single monomorphic ventricular extrasystoles (VES), totaling 622 per day. At the age of 12 years, according to the HM data, negative dynamics were observed, characterized by the appearance of polymorphic extrasystoles, paired extrasystoles, and unstable ventricular tachycardia, including polymorphic episodes with heart rates up to 162 beats per minute. At the age of 13 years, there was an increase in the representation of ectopic activity up to 8720 VESs per day, polymorphism of extrasystole, paired VESs and episodes of unstable ventricular tachycardia persisted.

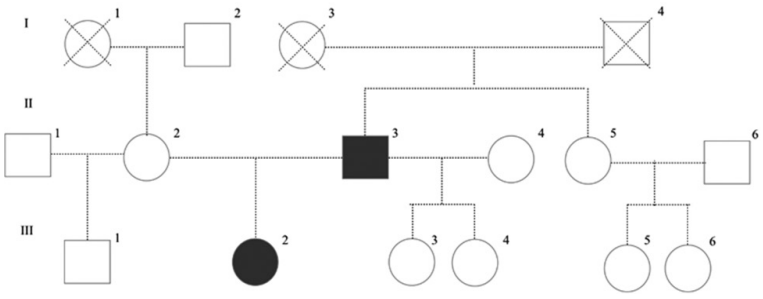

Fig. 2. Proband's pedigree (III2). I1 - died at age 52 years from breast cancer, I2 - arterial hypertension after age 60 years and lumbar disc herniation, I3 - died at age 53 years, underwent 2 mitral valve replacement surgeries and had a history of pancreatic cancer, I4 - arterial hypertension and heart disease unspecified, died at age 50 years. II2 - moderate joint hypermobility and skin hyperextensibility, open oval window, history of benign unilateral breast neoplasm, II3 - long-standing arterial hypertension, II5 - obesity and arterial hypertension, III5 - obesity, III6 - obesity.

First examined by us at the age of 14 years. The proband reported experiencing stabbing sensations in the heart area when agitated, dyspnea, and increased fatigue during moderate physical activity. Additionally, she described sensations of heart palpitations occurring 2-3 times a week, lasting 5-10 minutes, and accompanied by shortness of breath, which resolved spontaneously. No syncopal or presyncopal states were noted. The electrocardiogram (ECG) revealed sinus rhythm with a heart rate of 70-75 beats per minute, leftward deviation of the electrical axis of the heart, single polymorphic VES, episodes of bigeminy, anterior branch of the left bundle branch block, delayed intraventricular conduction, and a corrected QT (QTc) interval of 439-443 milliseconds. At echocardiography against the background of sinus rhythm with HR 62-73 per min and frequent VES, there was minimal aortic regurgitation, dilatation of the annulus fibrosus (AF) (2.42Z), mitral valve prolapse, thickening of the flaps and dilatation of the AF (2.48Z), moderate mitral regurgitation, mild tricuspid regurgitation, mild pulmonary regurgitation, FC dilatation (2.22Z), tendency to pulmonary trunk dilatation. The following was revealed: moderate LV dilatation, moderate LV dilatation, right chamber dimensions - within normal limits, impaired local contractility of LV myocardium, global LV systolic function was slightly reduced (LV ejection fraction according to Simpson 49%), right ventricular systolic function was preserved.

At HM - ventricular ectopic activity in the form of 25191 single polymorphic VESs in the average number of 1169 per hour, including insertion, episodes of bi- and trigeminal type, 1607 paired monomorphic and polymorphic VESs, 62 episodes of ventricular polymorphic accelerated rhythm / paroxysms of unstable ventricular polymorphic tachycardia with HR=89-238 per min lasting 1-7 seconds, 3 paroxysms of ventricular unstable monomorphic tachycardia with HR=151-226 per min (3 QRS). A total of 28634 ectopic ventricular complexes were recorded in a 24-hour period (24% of QRS complexes), a daily circadian type of arrhythmia. During the stress treadmill test, an unstable polymorphic ventricular tachycardia of 4 QRS with HR 230 per min was recorded at the third minute of stage 1. The proband underwent a selection of antiarrhythmic therapy, which consisted of the cardioselective β1-adrenoblocker atenolol in combination with the class 1C drug propafenone. This treatment regimen resulted in significant positive changes, including:A reduction in the representation of extrasystoles by more than 4 times, with 5,642 single and 98 paired polymorphic ventricular ectopic beats, as well as episodes of bigeminy type, averaging 246 per hour (6% of QRS complexes).Decrease in the number and duration of ventricular tachycardia episodes. Reduction in heart rate during tachycardia events, including 1 paroxysm of ventricular monomorphic tachycardia lasting 4 QRS complexes with a heart rate of 136 beats per minute, and 4 paroxysms of ventricular polymorphic tachycardia lasting 3-4 QRS complexes with heart rates ranging from 87 to 147 beats per minute. Therapy with angiotensin-converting enzyme inhibitors perindopril and aldosterone antagonist spironolactone was prescribed.

At the age of 15 years at the control examination, the proband complains of increased fatigue, low tolerance to physical exertion, weakness and occasional drowsiness. She denies syncope, but notes a single episode of dizziness accompanied by marked bradycardia and arterial hypotension. She receives therapy with propafenone, atenolol, perindopril and spironolactone with dose adjustment according to weight and examination data.

Body weight and height values greater than the 97th percentile (weight - 80.6 kg, height - 177 cm, BMI - 25.73 kg/m^2). Physical development is high, but disharmonious due to excess weight. A scoliotic posture disorder and a small funnel-shaped deformity of the thorax were noted. The following clinical features were also noted: high palate, bite disorder - orthodontic correction was performed, hyperextensibility and marbling of the skin, pronounced valgus deformity of the knee joints, flat-valgus setting of the feet, and joint hypermobility - 9/9 Beighton score (Fig. 3). At the time of examination, no osteoarthritis, spondylolisthesis, spondylosis, or other bone pathology was noted. Hepatomegaly, hyperinsulinism, and minor developmental anomalies such as trident, sandal-shaped cleft, and moderate clinodactyly of the fifth toes were observed.

According to ECG data, there is a slowing of atrioventricular conduction, impaired intraventricular conduction, impaired repolarization processes in the form of smoothed T teeth in standard and amplified leads. Slight prolongation of QT interval (in wedge position QTc = 438 ms, in orthostasis QTc = 475 ms).

According to the results of echocardiography: mitral valve prolapse with moderate mitral insufficiency, mild tricuspidal insufficiency, mild cor pulmonale insufficiency, minor LV dilatation persists. Global LV systolic function is insignificantly reduced, impaired local contractility of LV myocardium (anteroseptal hypokinesis) is noted. LA volume is at the upper limit of normal. The right chamber dimensions are within normal limits, while there is aneurysmal bulging of the anterior wall of the right ventricle in the projection of the middle third with myocardial thinning up to 2 mm.

Fig. 3. Photo of the proband: joint hypermobility (a), flat-valgus foot placement (b), posture disorder (c).

At HM, slowing of intraventricular conduction was registered, as well as polymorphic VES - single (total 4262), paired (total 83), and 2 episodes of unstable polymorphic tachycardia of 3 QRS with HR 100-117 beats/min. A mixed circadian type of arrhythmia was determined.

According to the results of magnetic resonance imaging, the mitral valve leaflets are thickened, and there is prolapse of the anterior leaflet into the LV cavity by 8-10 mm. The displacement of the posterior mitral valve leaflet attachment into the LV cavity by 13 mm, with «twisting» of the basal segment by 7 mm and hyperkinesis; mitral regurgitation 32 ml, regurgitation fraction 26% is also determined. The anterior wall of the RV is up to 3-4mm thick. An area of «bulging» of the wall with signs of dyskinesia is noted in the inflow part of the RV. Hypo- and dyskinesis in the posterolateral segment of LV with increased trabecularity at the level of the middle third, as well as increased LV myocardial extracellular volume in the posterolateral, posterior, posterior and anterior septal segments of LV at the middle level were noted. In the delayed phases of contrast enhancement, the accumulation of contrast agent along the trabecular part of the LV on the posterolateral segment of the LV at the level of the middle third is noted, consistent with fibroelastosis. Subepicardial accumulation of contrast agent in the posterolateral and posterior segments of LV at the basal level - changes of non-ischemic genesis - is also noted. The volume of fibrotic altered LV myocardium is about 3-4%.

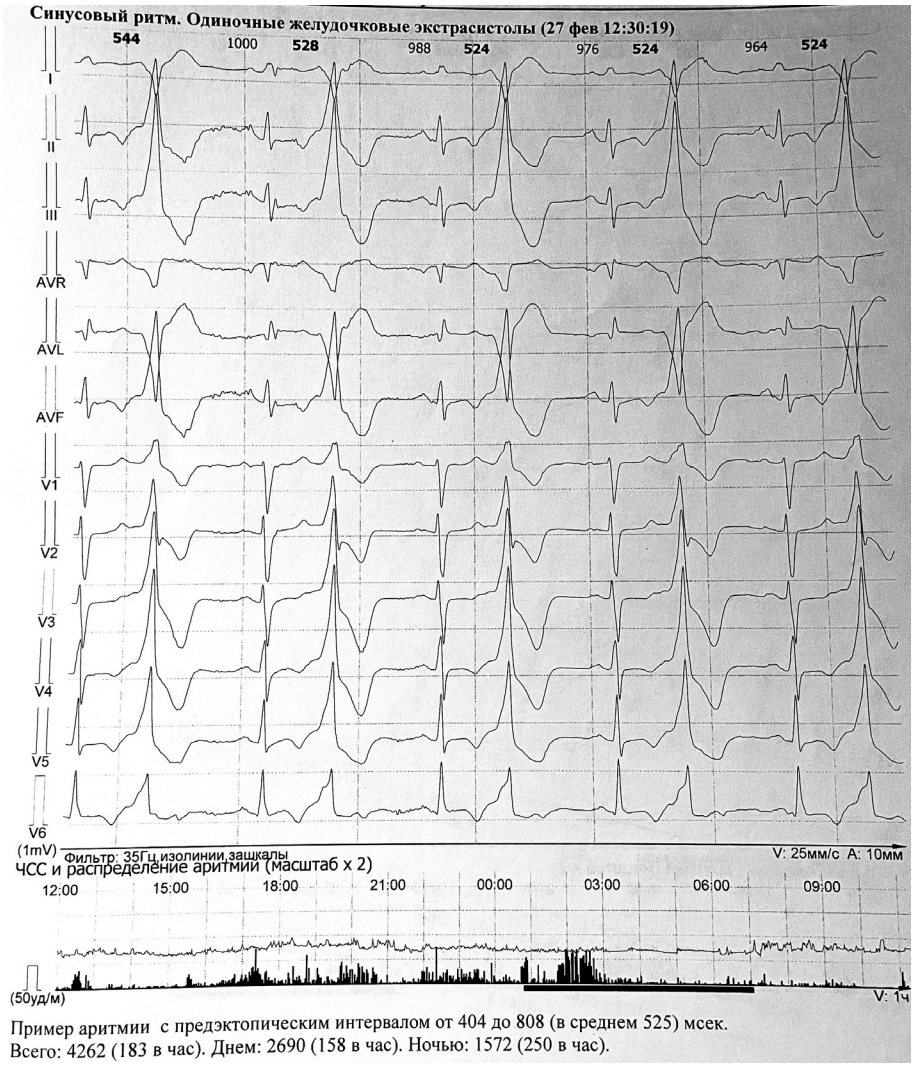

Fig. 4. Example of arrhythmia from the Holter monitoring report of the proband.

The proband has chronic heart failure of functional class II according to NYHA (dyspnea on exertion, episodes of dizziness). Due to the presence of a complex cardiac phenotype formed at an early age in the proband, together with extracardiac manifestations, genome sequencing was performed as a first-line study. Two genetic variants in two different genes, PKP2 and SMAD3, both in heterozygous state, not previously described in the literature, were detected (Table 1).

The variant in the PKP2 gene is located in the 1st of 13 introns of the gene (transcript ENST00000000070846.10) and results in the disruption of the donor splice site, c.223+2T>G. Pathogenic variants in the PKP22 gene lead to the development of ARVC type 9. The variant does not occur in the gnomAD v3 .1.1 population frequency database, is highly likely to result in splicing disruption as predicted by computer algorithms (SpliceAI, ada, rf)

Table 1.

The results of sequencing the proband's genome

Gene	Associated disease (OMIM phenotype number)	DNA modification (HG38) (protein change)	Zygosity (type of genetic inheritance)	Frequency
PKP2	ARVC, type 9 (609040)	12:g.32896507A>C ENST00000070846.10: c.223+2T>G	Heterozygote (dominant)	0
SMAD3	Loeys-Dietz syndrome, type 3 (613795)	15:g.67165336_67165337dup ENST00000327367.9: c.484_485dup ENSP00000332973.4: p.Asn163LysfsTer24	Heterozygote (dominant)	0

Note: hereinafter ARVC - arrhythmogenic right ventricular cardiomyopathy

and loss of function of the corresponding gene copy. The variant was classified as probably pathogenic according to the criteria of the American College of Medical Genetics and Genomics (ACMG) [17]. The criteria in favor of the pathogenicity of this variant were PVS1 (variant resulting in loss of function in a gene, where loss of function is the described disease mechanism), PM2 (variant does not occur in the population sample).

The variant in the SMAD3 gene is located in the 3rd of 9 exons of the gene (transcript ENSP00000332973.4) and is a duplication of two nucleotides c.484_485 resulting in a shift of the reading frame and the formation of a premature termination codon for protein synthesis (p.Asn163LysfsTer24). Pathogenic variants in the SMAD3 gene lead to the development of LDS3. The variant does not occur in the gnomAD v3.1.l population frequency database, with a high probability of resulting in loss of function of the corresponding gene copy. The variant was classified as probably pathogenic according to ACMG criteria [17]. The criteria in favor of the pathogenicity of this variant were PVS1 (variant resulting in loss of function in a gene, where loss of function is the described disease mechanism), PM2 (variant does not occur in the population sample).

To clarify the pathogenicity of the variants, their inheritance status was verified by analyzing the segregation of variants in the proband's family by Sanger direct automated sequencing. Both variants were found to be inherited from the proband's father (unavailable for clinical examination), who, according to the proband's mother, had unspecified cardiovascular abnormalities from a young age. It is also known from the mother's words that both parents of the proband's father had cardiovascular diseases that caused death before the age of 55.

DISCUSSION OF FINDINGS

In a proband with evidence of cardiovascular lesions, two previously undescribed in the literature probably pathogenic variants were found in heterozygous state, one in the *PKP2* gene and one in the *SMAD3* gene.

The variant in the *SMAD3* gene is a duplication in exon 3 of two nucleotides c.484_485 that results in a frameshift and the formation of a premature translation termination codon (p.Asn163LysfsTer24). When genetic variants located not in the last (or in some cases not in the penultimate) exon result in the synthesis of a premature translation termination codon, mRNA expressed from such an allele undergoes nonsense-mediated decay, a mechanism of mRNA «quality control». Early termination codons are recognized during the first translation of mRNA and trigger nucleolytic pathways for mRNA decay [18]. Because the variant in the *SMAD3* gene in the proband is located in exon 3 of 9, the mRNA product expressed from this allele is highly likely to undergo nonsense-mediated decay.

A variant in the *PKP2* gene located in intron 1 leads to disruption of the donor splice site c.223+2T>G, which is highly likely to result in frameshift and the formation of a premature translation termination codon due to splicing disruption, mRNA with this variant is also highly likely to undergo nonsense-mediated decay. Variants resulting in early termination codon, such as some variants resulting in frameshift, nonsense variants, and some variants resulting in splicing disruption, cumulatively account for 70-90% of all variants associated with the development of ARVC [19]. LV lesions occur in 18% of those with ARVC type 9, less frequently than in other types of ARVC [7]. However, LV myocardial damage in the form of its hypertrophy occurs in a part of patients with LDS3 [20]. It was probably the combination of the two diseases in the proband that led to the fact that ARVC manifested with active LV involvement.

According to the 2020 Padua Diagnostic Criteria, two major criteria for ARVC were obtained: unstable ventricular tachycardia with morphology of left bundle branch block; frequent VESs (Fig. 4). In addition, there is one incomplete major criterion, a LV aneurysm with-

Table 2.

Clinical manifestations observed in the proband and their relationship to LD syndrome type 3 and ARVC

Clinical manifestation	LDS, type 3	ARVC, type 9	Other
Ventricular extrasystoles	-	+	-
Ventricular tachycardia	-	+	-
QT interval prolongation	-	+	-
Dilation of the QRS complex	-	+	-
Aneurysmal bulging of the RV anterior wall	-	+	-
Fibrous ring dilatation*	+	-	-
Scoliosis	+	-	-
Funnel-shaped chest deformity	+	-	-
LA and LV dilatation	+	-	-
Disturbance of local contractility of LV	-	+	-
High palate	+	-	-
Bite disorder	+	-	-
Skin hyperextensibility	+	-	-
Valgus deformity of the knee joints	+	-	-
Valgus foot placement	+	-	-
Joint hypermobility	+	-	-
Hepatomegaly	-	-	+
Hyperinsulinism	-	-	+
Minor developmental anomalies[&]	-	-	+

Note: LDS, Lois-Dietz syndrome; ARVC, arrythmogenic right ventricular cardiomyopathy; * - aortic, mitral and pulmonary valves with associated regurgitation; LA - left atrium; LV - left ventricle; [&] - sandal-shaped slit, tridentate, clinodactyly of the fifth fingers/

out diastolic dysfunction or dilatation of the LV. There are also two minor criteria: end-activation QRS duration >55 (60 ms). Based on the molecular genetic study and information about the presence of cardiac pathology in the child's father, there is a high probability of ARVC in the girl's father.

Additionally, two major criteria of the left ventricular variant of arrhythmogenic cardiomyopathy are present in the patient's history: dilatation and a decrease in LV ejection fraction, with improvement observed with cardioprotective therapy; and accumulation of contrast agent along the trabecular part of the LV on the posterolateral segment at the middle third level, indicative of fibroelastosis. Three minor criteria are also noted: inversion of T waves in the left thoracic leads previously observed on ECG in the supine position (currently not detected in the supine position with ongoing therapy), inversion of the T wave in the left thoracic leads in the standing position and after exertion, and the presence of frequent VES and unstable ventricular tachycardia with morphology consistent with right bundle branch block. Thus, ARVC with biventricular lesion was diagnosed [21]. QT interval prolongation present in the proband is not part of the clinical criteria for ARVC but is often associated with ARVC and may be due to myocardial structural abnormalities [22].

It is worth noting that both ARVC and LD3 are more characterized by manifestation in adulthood - after 30 years of age. In our proband, the first manifestations of heart disease were detected apparently from the age of 5 years. It should be noted the presence of clinical manifestations that are not characteristic for either LD3 syndrome or ARVC (Table 2). We believe that a molecular link between *SMAD3* and *PKP2* gene products is highly likely to underlie such an early and atypical debut of ARVC in the proband.

This is supported by the description of several cases of ARVC type 1 phenotype associated with pathogenic variants in the *TGFB3* gene leading to overexpression of the TGF-β signaling pathway ligand gene and subsequent dysregulation of signaling, which presumably causes dysfunction of desmosomes that include placophyllin-2 [10, 23]. That is, impaired signaling through the TGF-β signaling pathway in a patient with pre-existing structural abnormalities of desmosomal proteins may contribute to exacerbating desmosomal dysfunction in the myocardium and accelerating cardiac tissue damage. Thus, increased signaling through the TGF-β signaling pathway resulting from dysfunction of one allele of the *SMAD3* gene also additionally has a negative impact on desmosome function. In addition, low expression level of plakophilin-2 leads to increased expression of *TGFB1* gene, which encodes TGF-β1 protein, one of the ligands of TGF-β signaling pathway [24]. That is, dysfunction of one allele of the *PKP2* gene further impairs signaling through the TGF-β signaling pathway.

CONCLUSION

Genome sequencing revealed in a proband with a complex phenotype including ARVC phenotype and LDS3 phenotype, two previously undescribed in the literature probably pathogenic variants in heterozygous state, one in the *PKP2* gene and the other in the *SMAD3* gene, associated with ARVC and LDS3 syndromes, respectively. Because the products of these genes are combined in the same molecular pathway, the combination of variants in the *SMAD3* and *PKP2* genes could conceivably lead to an amplification of each other's pathologic effects, and thus to a more severe phenotype and earlier manifestation than would be expected in isolated cases carrying the same genetic variants. Also noteworthy is the occurrence of clinical manifestations that are not characteristic of each of these diseases separately. Proband needs to be monitored in an expert medical center through a monitoring system with specialists - pediatric cardiologists and geneticists.

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