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A Review of Clinical Data of Family Form of Myofibrillar Desmin Myopathy

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ABSTRACT

Introduction: Desminopathy is a rare hereditary disease associated with a mutation in the *DES* gene, which is a type of myofibrillar myopathy. Damage to skeletal, cardiac, smooth muscles, as well as the diaphragm is possible with this disease. In clinical practice, desminopathy is a difficult diagnostic task.

Purpose of the study. Study of the dynamics of the clinical picture of myofibrillar myopathy with a mutation in the *DES* c.1021A> C (Thr341Pro) gene in a heterozygous state and analysis of the family tree.

Clinical description. A detailed analysis of the medical documentation of the patient's family along the father's side in the 6th generation with a case of desminopathy was performed. A family study in a total of more than 100 years is presented with a description of the dynamics of clinical manifestations, morphological, cardiological and electromyographic parameters.

Results. Weak skeletal muscle weakness in the proband and his father with desminopathy manifested itself at the age of 30, the last of which died of pulmonary heart disease 20 years after the manifestation of the disease. In the two older generations, 75% of relatives had heart problems at the seventh decade of life (n = 5: myocardial infarction, coronary heart disease, bradycardia - pacemaker installed) and / or oncological diseases (n = 6: malignant tumors of the prostate gland, skin, bladder (2 cases), uterus, rectum), who later died from these pathologies. The described case shows different clinical manifestations and is of interest in understanding the pathogenesis of a hereditary disease.

Conclusion. The obtained data can be used in the future for advanced research by neurologists, cardiologists, immunologists, oncologists, and geneticists in order to reveal the mechanism of the disease.

KEYWORDS: desmin, *DES*, desminopathy, myofibrillar myopathy, mutation, cancer, electromyography, heart failure

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INTRODUCTION

Desmin, an intermediate strand protein in striated muscle, is an important component of the muscle cell cytoskeleton [1]. The desmin gene (*DES*), which is localized on chromosome 2q35 encodes it [2].

Mutations in the human *DES* gene cause severe myopathies and cardiomyopathies [3-6], inherited in an autosomal dominant and autosomal recessive manner [7]. To date, many of these diseases remain undetected due to their diverse clinical presentation [8, 9]. Phenotypes of cardiomyopathy mainly include hypertrophic, dilated, restrictive and arrhythmogenic cardiomyopathies of the right ventricle [10].

Protein desmin is constantly in the focus of attention of scientists who study its changes associated with damage and muscle atrophy in various conditions [11]. Myofibrillar myopathies have common histological characteristics, including progressive disorganization of the myofibrillar network and protein aggregation [12-14]. The presence of mutant desmin causes multilevel mitochondrial damage [15], a general imbalance in skeletal muscle protein homeostasis through the aberrant activity of all major protein quality control systems [16]. Individual desmin mutations have unique pathological molecular mechanisms [17].

Most hereditary myopathies are clinically characterized by progressive muscle weakness [18-20]. A permanent violation of the cytoarchitecture of skeletal muscle at the level of one fiber may precede and be responsible for progressive muscle weakness.

The manifestation of desminopathy varies greatly and can be from the first to the eighth decade of life, and information on the preclinical stages of the disease is extremely small. Early changes in the disease are an important basis for future research on the effects of exercise and pharmacological interventions.

The purpose of the study was to study the dynamics of the clinical picture of myofibrillar myopathy with a mutation in the *DES* c.1021A> C (Thr341Pro) gene in a heterozygous state and to analyze the family tree.

CLINICAL DESCRIPTION

The revealed rare form of myofibrillar desmin myopathy prompted us to study the patient's family along the father's side (Fig. 1) and analyze in detail the course of the disease in relatives.

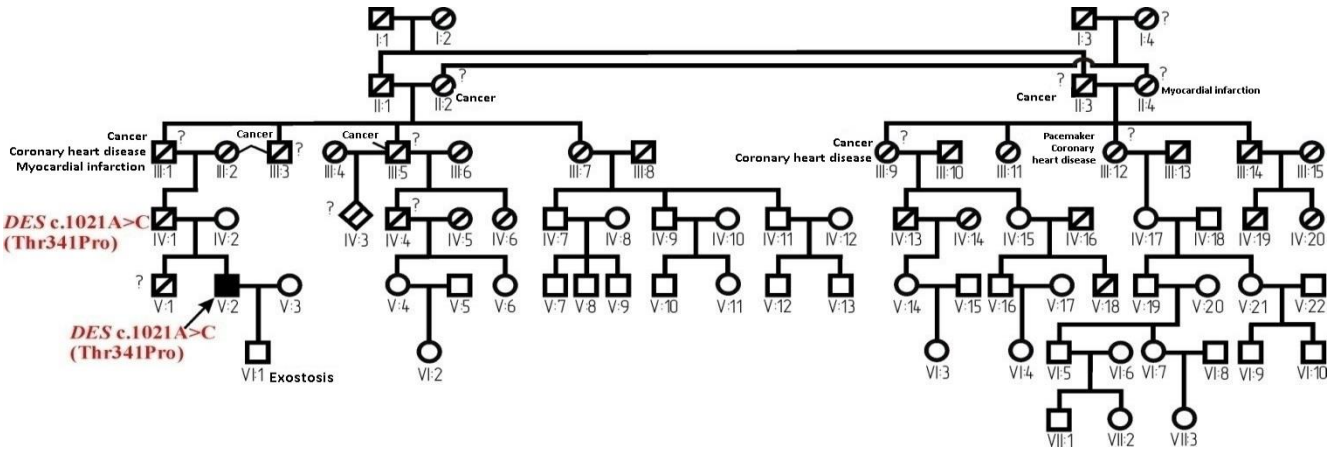

Figure 1. Pedigree of a family with hereditary myofibrillar desmin myopathy: shaded Figure V: 2 with an arrow - a sick proband; IV: 1 - sick proband's father; crossed out - dead; Roman numerals - generation; "?" - probably sick members of the pedigree.

Proband V: 2 was born from the second pregnancy, the first child (boy V: 1) died in utero at 7 months of pregnancy. Proband grew and developed by age, was actively involved in sports. At the age of 30, he noticed stumbling, muscle weakness and fatigue, mainly of the lower extremities, difficulty climbing stairs, and heart rhythm disturbances. The dynamics of the results of daily ECG monitoring are presented in Table 1. The probabilistic neurological status at 33 years: the tone of the hands is not changed, the tone of the legs is reduced, the strength in the hands is 5 points, in the feet of both legs 5 points, in the proximal sections 3-4 points, gait "duck".

Echocardiography (ECHO-KG) proband at age 34: cavity sizes, myocardial thickness, valve function unchanged; the size of the left atrium is 32 mm, the thickness of the interventricular septum is 9 mm, the size of the right ventricle is 23 mm, the left ventricle is 45 mm, the additional chord in the cavity of the left ventricle (LV), LV contractile function is satisfactory, ejection fraction is 67%.

The following clinical diagnosis was suggested by a proband at the age of 35 years on lower limb MRI: myofibrillar myopathy (desminopathy or αβ-crystallinopathy). Then, a proband DNA sample was studied by direct automatic sequencing and the substitution c.1021A> C (Thr341Pro) was found in the *DES* gene in a heterozygous state; no mutations were detected in the *CRYAB* gene. Next, DNA diagnostics ofproband's father IV:1 was carried out and a similar mutation was detected; proband'sson VI: 1 and proband'smother IV: 2 was not found.

ECHO-KG of proband at the age of 40: heart chambers are not expanded, myocardial contractility at rest is not reduced (ejection fraction 67%), myocardial shortening fraction is not reduced (FS - 37%), echoes of bradycardia, left atrial diastole size 36 mm, the thickness of the interventricular septum is 8.2 mm, the size of the right ventricle in diastole is 31 mm, the left ventricle is 48.1 mm, the valves are unchanged, the crescent is normal, valves without visible pathological changes, no additional formations were detected, no echo signs of local disturbance of contractility were detected.

The neurological status of proband at 38: muscle strength in the upper extremities in the left hand – 4 points, in the right – 3 points; in the proximal sections of the legs: flexors – 1 point, extensors – 3 points; muscle tone is diffusely reduced, hypotrophy of the muscles of the shoulder girdle, chest, anterior abdominal wall, thighs; deep reflexes from the upper extremities are living symmetrical, from the lower extremities - the knees are reduced, Achilles absent; there are no violations of sensitivity; moves slowly with a cane; disability group III. After two years, the reflexes of the proband have not changed, muscle strength is reduced, he moves slowly with the help of walking walkers, disability group II.

Father IV: 1 of proband, after graduating from the school, underwent two-year military service, successfully fulfilled the required physical standards. Complaints of weakness in the legs appeared at the age of 29 years. Then, during the examination, it was found that muscle tone is high, knee reflexes are high, Achilles are absent, there are no sensitive disorders, he cannot stand on his toes and heels, sways when walking, smokes since he was 18 years old. The diagnosis of infectious-allergic polyradioculoneuritis with lower flaccid paraparesis (feet) is suggested. At the age of 30, weakness in the legs increased, tone decreased, there was no atrophy, reflexes were reduced, the basic functions of the heart were not disturbed. Two years later, hyposthesia of the feet and legs appeared on both sides, and the feet have already begun to hang down. Biopsy data of the muscles of the father and proband are presented in Table 2.

During treatment, the condition of the father of proband was deteriorating. Neurological status at age 33: paretic gait with high leg elevation, sagging foot does not cling to the support, knee reflexes are sharply reduced, legs tone is reduced, abdominal reactions are alive, ladder standing, strength in arms is reduced to 3 points, more on the left, in legs to 2 points, muscle hypotrophy of both legs, tendon reflexes from the hands are reduced, hyposthesia of the left half of the face, legs like "stocking", on hands like "gloves", moves with a cane, group II disability. At age 34, a spinal muscular atrophy was mistakenly diagnosed. The dynamics of the results of needle electromyography (EMG) of family members is presented in Table 3.

From 41 years old, the father of proband moved in a wheelchair, group I disability. Severe hypotrophy of the distal upper and lower extremities was noted, pronounced paresis of the hands - 1 point, plegia of the feet, impaired function of the

pelvic organs by the type of rapid urination. The following year he suffered respiratory distress syndrome. Proband's father died from pulmonary heart disease (pneumonia) at the age of 49 years after 20 years the manifestation of the disease.

Proband'**grandfather** III: 1 from the age of 35 was periodically disturbed by epigastric pain (chronic gastritis with reduced secretion). At 48 years of age, acute catarrhal appendicitis was removed. At the age of 46, he had bilateral pneumonia; at 61 and 62 years old, he had left-sided pneumonia. At 58, he was diagnosed with coronary heart disease (CHD). The dynamics of changes in heart rate of family members with desminopathy is shown in Fig. 2. At 68 years of age, shortness of breath appeared, decreasing while lying down, angina of rest and tension of the II functional class, signs of chronic coronary insufficiency of the side wall, atherocardiosclerosis, IIA stage of circulatory failure were established

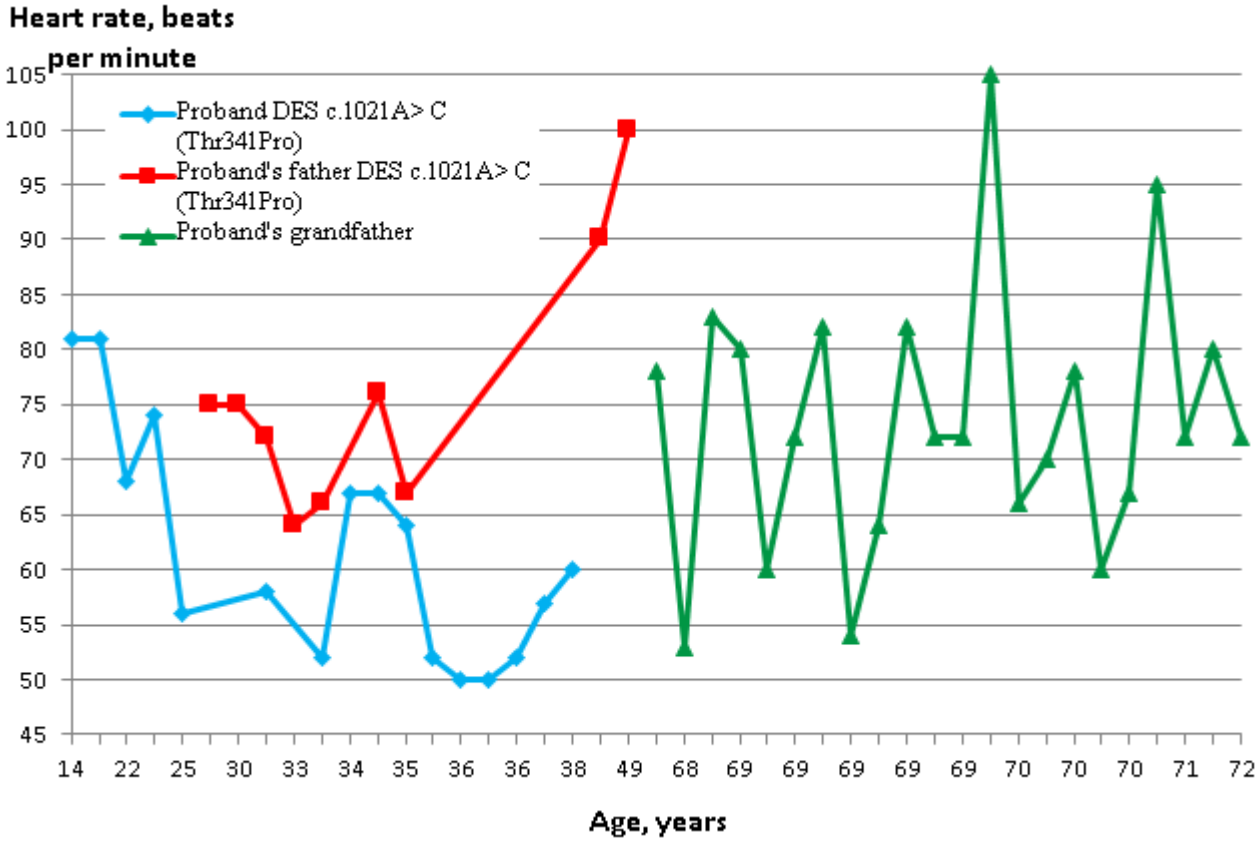

Figure 2. Dynamics of changes in the heart rate of family members with desminopathy

At 69 years old, the proband's grandfather experienced the first small focal recurrent antero-apical lateral with seizure of the septum myocardial infarction at night. At 70, a second myocardial infarction followed by progressive angina pectoris, post-infarction cardiosclerosis. At the same age, stage II rectal adenocarcinoma was detected (first manifestations at 67 years old). The 1st stage of intracavitary gamma therapy for the tumor was performed. A subsequent ECG of the heart recorded a sinus tachycardia of 95 beats per minute and metabolic disturbances in the myocardium. Stage 2 was stopped after a repeated attack of angina pectoris with metabolic disturbances, left ventricular myocardial hypoxia, signs of left ventricular hypertrophy, diffuse dystrophic changes. Proband'sgrandfather died at the age of 72 from rectal adenocarcinoma.

Proband's grandmother III: 2 died at the age of 88 from lymph node cancer. Elder sibling III: 3 of proband's grandfathers died at the age of 66 from prostate cancer. The middle sibling III: 4 of proband's grandfatherhad bladder cancer - he died at 65. His first child IV: 3 was born dead, the second son IV: 4 died at 73 years old as a result of cardiac arrest in a dream. Relatives IV: 6, IV: 13, IV: 20, V: 18 died as a result of accidents.

The older cousin III: 9 of proband's grandfather had ischemic heart disease, suffered from shortness of breath, died at the age of 78 from uterine cancer. Middle cousin III: 11 of proband's grandfather died at the age of 4 months.

The younger cousin III: 12 of proband's grandfather had a pacemaker installed at 68 years old due to bradycardia, shortness of breath and grade III AV block. However, DNA diagnostics did not find her replacement c.1021A> C (Thr341Pro) in the *DES* gene, but perhaps there were other desmin mutations. At 88, she had coronary artery disease, an angina of exertion of functional class III. ECHO-KG showed signs of aortic atherosclerosis, cardiosclerosis; a slight decrease in myocardial contractile function at rest (left ventricular ejection fraction - 52%); dilation of the left heart and cavity of the right atrium; aortic valve insufficiency of the II degree, tricuspid valve

insufficiency, pulmonary hypertension. She died at the age of 88 from heart failure.

Aunt II: 4 of proband's grandfather died at the age of 66 from myocardial infarction. Uncle II: 3 of proband's grandfather died of bladder cancer at 74 years old. Cousin I: 4 grandfathers proband died as a result of heart failure. Mom II: 2 of proband's grandfather at 80 years old was diagnosed with skin cancer - the tumor was removed, she died at the age of 89 years.

Exostosis was detected in proband's son VI: 1, but the DNA analysis did not detect a mutation in the *EXT1*, *EXT2* genes, and this disease is absent in both the proband's relatives and his spouse's relatives.

RESULTS

An analysis of the family tree of a family with desminopathy (Fig. 1) showed that in the 1st and 4th generations, two relatives died as a result of heart failure. 75% of family members (9 people) in the II and III generations died of cancer and / or heart disease. It should be noted that the grandfather of the proband and his two siblings (100% of men) died of cancer, respectively, at the age of 72, 65 and 66 years. In generations IV and V, the mutation c.1021A> C (Thr341Pro) was found in the *DES* gene in the father and proband. In the 6th generation, exostosis was revealed in the son of a proband, which suggests the presence of other mutations in the proband. We consider the presence of a large number of oncological diseases in this family not accidental.

Studies have shown that at the preclinical stages and at the onset of the disease, the proband had ventricular extrasystole (Table 1), later AV blockade appeared and pathological supraventricular arrhythmias were recorded. The nature of heart rate changes in the proband and his father in one age interval strikingly coincides (Fig. 2), but the pulse in the proband is lower (bradycardia). With the progression of the disease, proband has an increase in heart size while maintaining an ejection fraction of 67%. Grandfather proband suffered two myocardial infarctions at 69 and 70 years old, coronary heart disease was also found in his cousins, and the youngest at 68 years old had a pacemaker. A probable cause of heart failure in older family members could be isolated desmin cardiomyopathy.

A muscle biopsy of the father showed gross structural changes (Table 2), in contrast to the proband biopsy. At the initial stages of the disease, EMG (Table 3) did not record spontaneous activity in the father's muscles (at 29 years old) and proband (up to 33 years old), in addition, at the last stage, single fasciculation potentials recorded earlier disappeared at 34.5 years old. Desminopathy progresses more slowly in proband than in father, with so far no hyposthesia.

The described case shows different clinical manifestations and is of interest in understanding the pathogenesis of a hereditary disease.

CONCLUSION

Due to the low prevalence of myofibrillar desmin myopathy in a population, the diagnosis of this disease is a difficult task for a neurologist. An MRI of the muscles, determining the extent of their damage, suggests and, subsequently, confirms at the genetic level the diagnosis of neuromuscular disease. Studies have revealed the dynamics of the clinical picture of a family case of myofibrillar myopathy with a mutation in the *DES* c.1021A> C gene (Thr341Pro) in a heterozygous state. It was established that the cause of death of relatives along the line of the father of proband in most cases was cancer and / or heart disease. The obtained data can be used in the future for advanced research by neurologists, cardiologists, immunologists, oncologists, and geneticists in order to reveal the mechanism of the disease.

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Table 1. The dynamics of the results of daily monitoring of ECG of proband with desminopathy

Age, years	The results of daily monitoring of proband ECG *DES*c.1021A>C (Thr341Pro)
30	Ventricular extrasystole 1 gradation according to Laun.
34	Single ventricular extrasystoles of the 1st type - 5; Type 2 - 3; paired ventricular extrasystoles - 16; group ventricular extrasystoles - 4; single supraventricular extrasystoles - 80. Ischemic ECG changes were not detected. Exercise tolerance is moderate.
35	Normal circadian heart rate profile; 1 single atrial extrasystole, 1 single blocked atrial extrasystole recorded per day.
38	Transient atrioventricular block 2 degrees, Mobitz 1 with Samoilov-Wenckebach periods mainly at night, no ST segment dynamics were detected, pathological supraventricular arrhythmias are recorded. Ventricular extrasystole was not detected. Ischemic ECG changes were not detected.
40	3 monomorphic monotopic single ventricular extrasystoles; 1877 clinically significant pauses lasting more than 2.0 seconds, with a maximum of 3.184 seconds due to AV blockade of degree 2 of type 1, with episodes of blockade of 2: 1. Authentic Depression c. ST more than 1 mm. not found.

Table 2. The results of histological studies of muscle tissue of the family with c.1021A> C mutation (Thr341Pro) in the *DES* gene

Father of proband	Proband
Biopsy of the muscle of the left leg in 33 years: gross structural changes with severe atrophy of muscle tissue and its replacement with fat and connective tissue with a clear predominance of fat. In the muscle-connective tissue bundles, proliferation of endomysium elements is noted. There is no inflammatory infiltration in the tissue.	Biopsy of the 4th head of the thigh muscle at age 35: striated muscle tissue without gross structural changes. There is no inflammatory infiltration. There are small layers of adipose tissue between the muscle bundles. There is no muscle atrophy characteristic of polyneuritis. Mild dystrophic changes in muscle fibers.

Table 3. Dynamics of the results of needle electromyography of family members with mutation c.1021A> C (Thr341Pro) in the *DES* gene

Age, years	Proband's father	Proband
29*	Anterior activity not found.	-
33*	Unstable spontaneous activity from the muscles of the shoulder girdle, on the lower extremities is not determined. The amplitude of oscillations in the distal muscle groups of both legs was sharply reduced with arbitrary contraction.	No spontaneous activity was detected. The interference curve of the deltoid muscles within the normal range in frequency and amplitude, and the calf on the right - is reduced in amplitude and discharged in frequency. The amplitude potential of the motor units of the muscles is normal, the duration of the potential of the motor units of the deltoid muscles is shortened by 19%, the calf muscle is normal. IIIa EMG Stage denervation-reinnervation process is recorded by histograms of deltoid muscles and IIIb EMG stage denervation-reinnervation process, with compensatory reinnervation is recorded by histogram of the calf muscle.
34**	-	Signs of the current denervation process, pronounced in the distal muscle of the leg, were revealed in all muscles. The amplitude of the potential of motor units is increased. Single fasciculation potentials are recordedin all muscles.
34	-	Violent spontaneous activity persists in the distal muscle of the leg, and the potentials of fasciculations disappear. In the proximal leg muscle, the

, 5 * *		severity of spontaneous activity slightly increased, small potentials of motor units appeared, due to which the average amplitude of the potential of motor units decreased.
3 5 *	-	Spontaneous activity in the femoral muscle in the form of irregular low-amplitude fibrillation potentials. The duration of the potential of the motor units of the deltoid muscle is shortened by 23.1% (previously by 19%), the amplitude of the potential of the motor units is increased by 33.8%, polyphasia is 85% (previously 90%), the positive acute waves are single, low-amplitude; II EMG stage of denervation-reinnervation process is recorded, earlier IIIa EMG stage of the denervation-reinnervation process. The duration of the potential of the motor units of the gastrocnemius muscle is shortened by 19.2% (previously normal), the amplitude of the potential of the motor units is increased by 88% (previously by 83%), polyphase 50% (previously 50%); According to the histograms, IIIa EMG stage is a denervation-reinnervation process, earlier IIIb EMG stage.
3 5 , 5 *		Spontaneous activity from the gastrocnemius muscle in the form of rhythmic potentials of fibrillation and a sudden discharge of the "giant" potential of the motor units. The interference curve of the deltoid muscle within normal limits in frequency is reduced in amplitude; the rectus femoris muscle is reduced in amplitude, discharged in frequency. According to the histograms, in the deltoid muscle of II EMG, the stage of the denervation-reinnervation process; polyphasia in the deltoid muscle - 90%, in the femoral rectum -70%, gastrocnemius -95%. The duration of the potential of the motor units of the deltoid muscle is shortened by 26.4%, the femoral straight by 18.1%, and the calf by 12.5%. Amplitude increased by 98%, 57% and 98.7%, respectively.

* - the studies were performed in dynamics by doctor No. 1;

** - the studies were performed in dynamics by doctor No. 2.