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LMNA-КАРДИОМИОПАТИЯ ПРИ МЫШЕЧНОЙ ДИСТРОФИИ ЭМЕРИ-ДРЕЙФУСА

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LMNA-Cardiomyopathy in Emery-Dreifuss Muscular Dystrophy

Резюме

Мышечная дистрофия Эмери-Дрейфуса — редкое заболевание, возникающее вследствие генетического дефекта белков ядерной оболочки, чаще эмерина и ламина А/С. Заболевание проявляется медленно прогрессирующей слабостью лопаточно-плечевой и тазово-перонеальной групп мышц, миодистрофией, первичной контрактурой суставов, а также кардиомиопатией с нарушениями ритма и проводимости. Сердечно-сосудистые осложнения и жизнеугрожающие аритмии — основная причина смерти таких пациентов в молодом возрасте. В зависимости от ведущих симптомов и наследственного анамнеза больные попадают в поле зрения разных клиницистов — неврологов, кардиологов, аритмологов, ортопедов, — часто недостаточно информированных о данном заболевании, что препятствует диагностике, своевременной профилактике и лечению осложнений. В данной статье рассмотрены данные эпидемиологии, патофизиологии, особенности течения, диагностики, подходы к ведению сердечно-сосудистой патологии при прогрессирующей мышечной дистрофии Эмери-Дрейфуса с развитием LMNA-кардиомиопатии. А также представлен клинический случай данного заболевания.

Ключевые слова: *Эмери-Дрейфуса, кардиомиопатия, ламинопатия, LMNA, мышечная дистрофия*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Emery-Dreifuss muscular dystrophy is a rare disease resulting from a genetic defect in nuclear envelope proteins, most commonly in emerin and lamin A/C. The disease is characterized by slowly progressing weakness of the scapular-brachial and pelvic-peroneal muscle groups, myodystrophy, primary joint contracture and cardiomyopathy with rhythm disorders and conduction abnormalities. Cardiovascular complications and life-threatening arrhythmias are the main cause of death in such patients at a young age. Depending on the leading symptoms and family history, patients are under the care of different specialists. Unfortunately, neurologists, cardiologists, cardio surgeons and orthopedics are not well informed about this rare condition and thus the disease tends to be not diagnosed in time. This article examines the data of epidemiology, pathophysiology, features of the course, diagnosis, approaches to the management of cardiovascular pathology in progressive Emery-Dreyfus muscular dystrophy with the development of LMNA cardiomyopathy. A clinical case of this disease is also given.

Key worlds: *Emery-Dreifuss, cardiomyopathy, laminopathy, LMNA, muscular dystrophy*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «LMNA-Cardiomyopathy in Emery-Dreifuss Muscular Dystrophy» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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AV — atrioventricular, SCD — sudden cardiac death, DCMP — dilated cardiomyopathy, LTVT — life-threatening ventricular tachyarrhythmia, ICD — implantable cardioverter defibrillator, CMP — cardiomyopathy, MAPK — mitogenic-activated protein kinase, MRI — magnetic resonance imaging, ACVA — acute cerebrovascular accident, CF — cardiac failure, CVC — cardiovascular complications, CRT– cardiac resynchronisation therapy, AF — auricular fluttering, TEC — thromboembolic complication, LV EF — left ventricle ejection fraction, AFib — atrial fibrillation, Holter ECG — Holter electrocardiography monitoring, CCF — chronic cardiac failure, EDMD — Emery — Dreifuss muscular dystrophy, ECG — electrocardiography, ECS — electrocardiostimulator, EchoCG — echocardiography

Introduction

In the 1960s, two neurologists — E. E. Emery and F. Dreifuss — identified a unique group of patients with a hereditary muscular-cardiac-articular syndrome. When compared to the previously described Duchenne — Becker muscular dystrophies, the clinical course of this condition was more benign [1]. The syndrome was called Emery — Dreifuss muscular dystrophy (EDMD). The following symptom triad is typical for this dystrophy:

1. Slowly progressing dystrophies and weakness of scapular, shoulder and fibular muscles, which usually manifest at the age of 3 to 15 years old. The ability to walk independently is lost in extreme cases [2].
2. Early contractures in elbow flexors, Achilles tendon flexors and neck extensors. The latter are often observed during the first decade of life, but get worse and cause discomfort in adolescence [3].
3. Clinically, heart involvement manifests during the 2nd or 3rd decade of the patient's life. The most often manifestations are atrial and ventricular tachyarrhythmia, conduction abnormalities, cardiomyopathy (CMP) with developing cardiac failure (CF). The incidence of CF can exceed 60 % in patients over 50 years of age with *LMNA* gene mutations [4]. Cardiac manifestations can precede skeletal muscle weakness. If compared to the general population, female EDMD carriers have a higher risk of cardiovascular complications (CVC) even in the absence of marked neural and muscular symptoms [1].

Pathogenesis

The pathogenesis of EDMD is associated with protein-coding genes: emerin — gene *EMD*, lamin — *LMNA*, nesprin 1 — *SYNE1*, nesprin 2 — *SYNE2*, H-like protein 1 factor — *FHL1*, transmembrane protein 43 — *TMEM43*. They correspond to the specific EDMD subtypes: EDMD 1 (gene *EMD*), EDMD 2 (*LMNA*), EDMD 3 (*LMNA*), EDMD 4 (*SYNE1*), EDMD 5 (*SYNE2*), EDMD 6 (*FHL1*), EDMD 7 (*TMEM43*) (Fig. 1) [5,6].

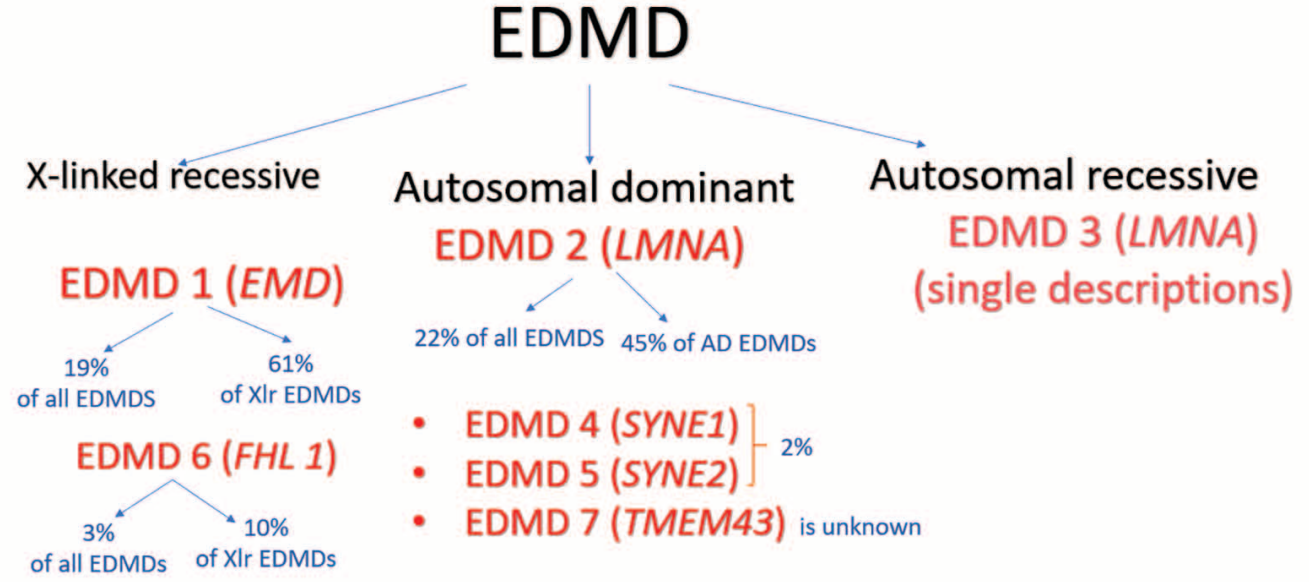

Figure 1. *7 genetic variants of Emery-Dreifuss muscular dystrophy.*
Note: EDMD — Emery-Dreifuss muscular dystrophy, EMD — emerin protein genes, LMNA — lamin protein gene, SYNE1, SYNE2 — genes of proteins nesprin-1, nesprin-2, respectively, FHL1 — gene factor H-like protein 1, TMEM43 — transmembrane protein 43. Xlr — X-linked recessive, AD — autosomal dominant

According to the Online Mendelian Inheritance in Man (OMIM) database, genes *SUN1, SUN2*, which encode homonymous proteins of the internal nuclear membrane, and *TTN* (titin-encoding gene) are also potentially associated with EDMD phenotype [7]. Mutations in genes *LMNA* and *EMD* are the most common causes of EDMD; they account for approximately 40 % of EDMD cases [2].

In 1986, when the first gene *EMD* responsible for the disease development was discovered, the molecular era of EDMD diagnostics began. Mutation in this gene causes impaired production of emerin, with the X-linked mode of inheritance [6,8].

In 1999, it was discovered that EDMD 2 is related to gene *LMNA*, localised on the long arm of chromosome 1 (q11–q230. Mutations in this gene cause defects in the structure and function of lamin A/C and clinical manifestations of EDMD; usually, the mode of inheritance is autosomal dominant [6,9].

Lamins A/C and emerin are nuclear membrane proteins and components of the nuclear lamina, which participates in the maintenance of the cellular architecture and is a frame for other factors, which participate in deoxyribonucleic acid replication, chromatin organisation and transcription [10]. Atrioventricular (AV) node cells, which do not contain lamin A, demonstrate increased nuclear deformity and apoptosis [11]. A cascade to destroy pacemaker cells and cardiac cells is triggered, resulting in gradual replacement of the myocardium with fibrous and fatty tissue. The process usually starts in atria, then involves AV node and, finally, ventricles (Fig. 2) [2].

Lamin A/C defect is characterised with a wide clinical variability, genetic heterogeneity, variety of phenotypes. In addition to EDMD2, mutations in gene *LMNA* are responsible for the development of over a dozen of diseases — laminopathies, involving various tissues (skeletal muscles, myocardium, fatty tissue, peripheral nerves), both individually and systemically (premature ageing syndrome) [12]. Cardiac manifestations of laminopathies are versatile: dilated CMP (DCMP), restrictive CMP, conduction abnormalities, atrial fibrillation/fluttering (AFib/AF), malignant ventricular arrhythmias [13,14].

Potential mechanisms of LMNA-CMP pathogenesis:

- Haploinsufficiency (one gene copy is not enough for normal protein function, where inactivation of even one of the two alleles can cause disease), which results in early death of AV node cardiac cells.
- Abnormal chromatic organisation.
- Abnormal activation of mTOR path (rapamycin target in mammals — serine/threonine kinase, participating in control of cell growth and proliferation).
- Abnormal activation of the platelet growth factor path, which results in impaired calcium metabolism [15-17].

Very often, the degree of cardiac involvement in EDMD does not correlate with the muscle weakness progression. Patients with a mild skeletal muscle damage can have severe conduction abnormalities, requiring an implantable electrocardiostimulator (ECS). Individuals with gene *LMNA* mutations often have severe DCMP and life-threatening rhythm and conduction abnormalities [18].

EPIDEMIOLOGY

This disease is rare; it affects 0.39 per 100,000 (1 per 250,000) people (Table 1) [19,20].

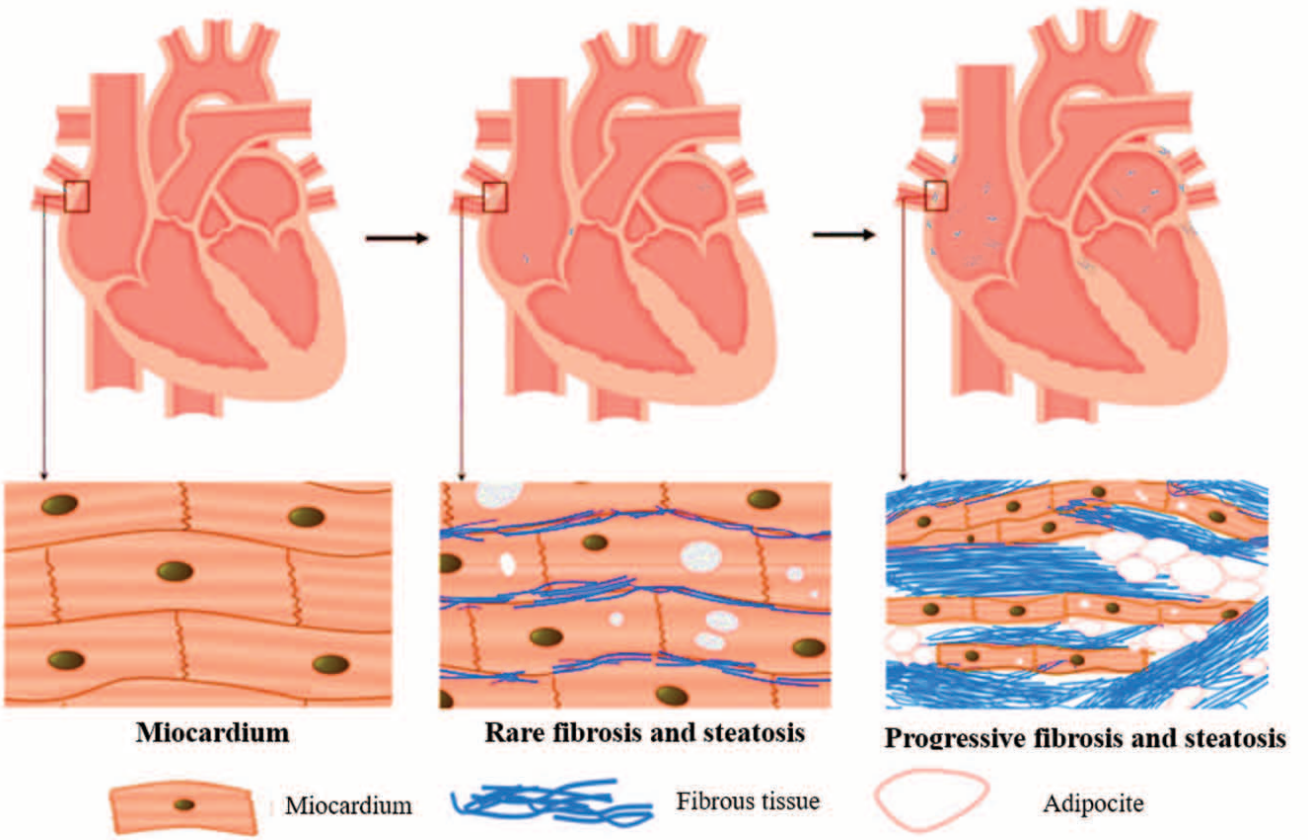

Figure 2. *Replacement of atrial myocardium by fibrosis and adipose, which can eventually affect atrioventricular node and ventricle [2]*

Table 1. *The prevalence of various types of EDMD [5,20].*

Types	Frequency of occurrence
EDMD 1	0.13 — 0.2 per 100 thousand 19 % of all EDMD
EDMD 2	22 % of all EDMD
EDMD 3	10 registered cases
EDMD 4	2 % of all EDMD
EDMD 5	
EDMD 6	3 % of all EDMD
EDMD 7	is unknown

Note: EDMD — Emery-Dreifuss Muscular Dystrophy

Diagnosis

EDMD diagnosis can be challenging due to the low incidence of this condition and similarity with other muscle dystrophies and laminopathies [13, 21].

If a muscle dystrophy is suspected, electroneuromyography and muscle biopsy are indicated; however, in EDMD and other laminopathies, results of these examinations are usually non-specific [14, 22].

An important marker of muscle dystrophies is high creatine phosphokinase levels, which can vary from normal values to 5–15-fold increase over the upper limit of normal. In patients with mostly heart involvement, creatine phosphokinase levels are within the normal range. In other words, increased creatine phosphokinase levels can be useful for the diagnosis, but normal levels do not rule out EDMD [2].

Skeletal muscle imaging can be a useful additional diagnostic tool. EDMD is characterised with scapular, shoulder and fibular muscle hypotrophy, while compensatory hypertrophy of muscles in other locations is not typical. Muscle imaging observations can contribute to the diagnosis of various muscle dystrophies [23-25].

All patients with EDMD should undergo a thorough examination of their cardiovascular system, including physical examination, ECG and Echo-CG, as well as Holter ECG monitoring [2, 14, 26-28].

ECG abnormalities in EDMD patients include atrial arrhythmias, AV arrhythmias, AV blocks. Common events are tachyarrhythmias: AFi, AF, other supraventricular and ventricular arrythmias [2]. Progressive conduction abnormalities up to complete transverse block are a common observation [29, 30].

Lazarte J., et al. (2022), who analysed the data from the UK Genetic Biobank using whole-genome sequenc-

ing (n = 185,990), found out 1,167 (0.63 %) patients with various gene *LMNA* mutations. The demonstrated the correlation between defects in lamin A/C protein and arrhythmias (AFib, bradyarrhythmias, ventricular arrhythmias, DCMP and CF (risk ratio (RR) = 2.21; p < 0.001). The incidence of arrhythmias or CMP was 43 per 1,000 person-years among carriers of defective gene *LMNA*, and 6.38 per 1,000 person-years among other, p < 0.001 [31].

EchoCG in EDMD can show DCMP. Signs of ventricular dystrophy from fibrosis can be observed. A common observation is enlarged atria as compared to ventricles, especially at early stages of diagnosis [26, 32].

Very often, magnetic resonance imaging (MRI) of the heart in patients with EDMD is not possible due to the presence of ECS.

Myocardium biopsy can show advanced atrial fibrosis, which causes EDMD. A study involving 8 patients with EDMD 2 showed the absence of any marked displacing fibrosis at Gd-enhanced MRI [32]. Heart MRI is usually used to visualise ventricles and is not widely used for atrial visualisation because adequate image resolution in thin-wall atria is impossible. In Duchenne muscular dystrophy, MRI is recommended for identification of ventricle myocardial fibrosis, which is an early sign of myocardial involvement preceding systolic dysfunction [33].

The gold standard in the diagnosis of EDMD is genetic testing, although currently it is not included in mandatory medical insurance programs. The majority of genetic tests are a sequencing analysis of a set of EDMD-associated genes, using NGS (next-generation sequencing) [34, 35].

Risk of sudden cardiac death

There are no specific scales to calculate the risk of sudden cardiac death (SCA) in patients with LNMA-CMP. In 2019, a validated scale to assess a 5-year risk of life-threatening ventricular tachyarrhythmia (LTVT) in laminopathies was developed (https://lmna-risk-vta.fr) [36]. Predictors are independent risk factors: male sex, gene *LMNA* mutation, AV block of grade 1 or above, unstable ventricular tachycardia and left ventricle ejection fraction (LV EF) of < 45 % [37]. In this scale, the 5-year estimated risk threshold of ≥ 7 % can predict 96.2 % of LTVT [36].

Wahbi K., et al. (2019) demonstrated that in patients with laminopathies (n = 444, of which 65 had EDMD), 19.3 % (n = 86) had LTVT (3.9 % of the annual morbidity; 95 % confidence interval (CI): 3.03–4.69) over a mean follow-up period of 3.6 years. Among patients with LTVT, 36 % (n = 31) had an implantable cardioverter defibrillator (ICD), 16 % (n = 14) had SCD [36,38].

Nakajima K., et al. (2018) showed that among 110 patients with gene *LMNA* mutations (60 families with laminopathies), 20 % were diagnosed with chronic CF (CCF) with LV EF of < 50 % during the first visit and in 52 % over a period of 5 years. Malignant ventricular arrhythmias (persistent ventricular tachycardia, ventricular fibrillation, SCD, ICD activation were diagnosed in 18 % during the first visit and in 42 % over a period of 5 years. 26 families (43 % of patients with laminopathies) had SCD events. Over the 5-year follow-up period, 17 deaths were recorded (19 % of patients with laminopathies), including SCD — in 4 (4 %), death caused by CF progression — in 13 (14 %), acute cerebrovascular accident (ACVA) — 1 (1 % of patients with laminopathies). It demonstrates a very unfavourable prognosis in LMNA-CMP [35,37,39].

Management

Management of patients with *LMNA*-CMP and EDMD 1 includes:

- Prevention and therapy of CVC.
- Prevention of skeletal myopathy progression, including rehabilitation exercises, mobility support and rehabilitation.
- Contracture surgery [13].

Management of patients with heart damage depends on the clinical presentation and complications.

Patients with CCF

In 2017, information appeared on the drug therapy of CF in EDMD and other neuromuscular conditions; it was concluded that the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are justified. Restricted use of beta blockers due to a high rate of AV blocks was mentioned [25,27].

In 2023, data were published on the efficacy of angiotensin II receptor antagonists and neprilysin inhibitors, sodium-glucose linked transporter 2 (SGLT-2) inhibitors in CCF in patients with *LMNA*-CMP. Reverse remodelling of left ventricle with the use of these products has been demonstrated in patients with isolated *LMNA*-DCMP [14].

Risks of TEC

One study in patients with laminopathies (n = 76) demonstrated a high incidence of atrial arrhythmias, especially AFib, which often precede ventricular dysfunction. The risk of thromboembolic complications (TEC) in patients with various abnormal variants of gene *LMNA*, including EDMD 2, is higher than in other DCMP (n = 224) (RR = 4.8, 95 % CI: 2.2-10.6; p < 0.05) [40].

Tremblay-Gravel M., et al. concluded that the high rate of AFib and higher risks of TEC in patients with *LMNA* gene mutations are a result of internal atrial myopathy [41]. Therefore, it is essential to follow the recommendations for AFib and AT in such patients. The efficiency of antithrombotic prevention in EDMD has not been studied; however, a high risk of cardioembolic strokes requires adequate prevention [42,43].

Heart rhythm and conduction abnormalities: ICD, ECS, CRT

According to the recommendations of the American Heart Association, ECS implantation is indicated in patients with EDMD with any grade of AV block, including grade one block, because of progression to complete AV block [44].

Currently, there are no clear recommendations on the use of antiarrhythmic drugs and ablation for ventricular arrhythmia in patients with *LMNA*-CMP. Given the location of substrate and a high risk of arrhythmia recurrence, no ablation for ventricular arrhythmia is indicated in these patients [45]. Sidhu K., et al. followed up patients with *LMNA*-CMP with implantable cardioverter defibrillators for primary (n = 27) or secondary (n = 16) prevention for two years. The incidence of ventricular tachycardias was significantly higher in patients with ICDs implanted for secondary prevention (28 ± 40.9 vs. 3.6 ± 7.3 episodes per 100 patient-years; $p < 0.001$) [46].

In patients with LMNA-EDMD, cardiac resynchronisation therapy (CRT) is also used, although due to its rareness the efficacy and safety in EDMD is understudied [44]. Sidhu K., et al. conducted a retrospective analysis of CRT results in patients with *LMNA*-CMP (n = 105, mean age: 51 ± 10 years). The factor, indicating positive response to CRT, was an increase in LV EF of ≥ 5 % in six months after implantation. Six months after CRT, the mean change in LV EF was 4 ± 9 %. Positive effects of CRT were observed in 38 % and were associated with a lower baseline LV EF (≤ 45 %) or high pre-CRT pacing rates (≥ 50 %) of the right ventricle in patients with an implanted ECS. In patients, who underwent CRT in strict compliance with the recommendations of the European Society of Cardiology (class I), the rate of response was 61 %. Median expected difference in survival without cardiovascular events in SRT responders was 1.3 year ($p = 0.04$). Thus, it has been demonstrated that in patients with LMNA-CMP CRT contributes to improved systolic function of LV, provided there are clear indications for implantation and survival rates [47].

Heart transplantation

Heart transplantation was described in patients with EDMD with terminal CF [48, 49]. However, heart transplantation or implantation of devices, which support LV function, in LMNA-CMP usually is not performed due to arrhythmogenic complications [48].

Promising pathogenetic methods of LMNA-CMP therapy

Currently, new promising treatment methods for patients with laminopathies have been investigated, which is possible to better diagnosis of this pathology [50]. Animal models are used to study a possible impact on mitogenic-activated protein kinase (MAPK), the pathological potential of which has been proven to increases in *LMNA gene mutations*. MAPK inhibitors have demonstrated favourable effects in mice models. In 2023, phase 2 clinical trial of low-molecular selective inhibitor of MAPK p38a — ARRY-371797 (PF-07265803) — was completed. The study evaluated the impact of the medicinal product on the functional performance of the patient and cardiac function in patients with *LMNA*-associated DCMP. Patients (n = 36) with NYHA class II–III CF were treated with ARRY-371797 100 or 400 mg twice daily for 48 weeks. The investigational medicinal product demonstrated positive results: increased functional performance of the patients and reduced concentrations of natriuretic peptide. In other words, MAPK p38a inhibition with this medicinal product can bring about a new therapeutic approach in the management of *LMNA*-CMP. Currently, a double-blind randomised placebo-controlled phase 3 study (REAL-DCM) is ongoing, which evaluates the impact of ARRY-371797 therapy on the functional performance, cardiac biomarkers and quality of life of patients with LMNA-DCMP [51].

Case Study

Until the age of 3 years old, the patient had been developing according to her age. Since the age of 3 years old, the patient had progressing gait disorder, shank and foot muscle weakness (Fig. 3). Spinal muscular atrophy was diagnosed. Then myopathy symptoms slowly progressed. Since the age of 8 years old, the patient had elbow contractures. At 11 years old, the patient started using a wheel-chair. At 14 years old, she also started having ankle joint contractures, at 20 years — knee and hip contractures, mostly on her right side.

In 2008, when the patient was 24 years old, she was diagnosed with paroxysmal AFib (150–160 bpm) for the first time. Initially, the patient had occasional paroxysm episodes once every half-year, which were treated with amiodarone. After a while, AFib episodes were more frequent; in 2015 to 2016, she was treated with cordarone, which resulted in thyrotoxicosis; for two years, she was treated with tyrosol. Since 2018, the patient has had permanent AFib. Due to a villus rectal polyp and potential haemorrhagic complications, the patient decided to withdraw from anticoagulants. Since she had acute essential oedema as a reaction to metoprolol succinate, the patient refused to take other beta blockers and was treated with ivabradine 5 mg.

At the age of 27 years old, in 2011, the patient underwent a clinical genealogical examination and DNA testing: c.745C> T mutation in gene *LMNA* was diagnosed. Hereditary history: her father had had similar symptoms since the age of two years old, and died at 27 years old from an acute cerebrovascular accident. Taking into account phenotype data, a hereditary history and DNA testing results, the following diagnosis was made: Progressing Emery — Dreifuss muscular dystrophy, autosomal dominant mode of inheritance.

Figure 3. *Patient's photo to 4 years old: she is able to walk independently, the beginning of manifestations of muscle weakness (All materials are posted with the patient's consent)*

In 2016, ECG showed grade 1 AV block. Holter ECG showed periods of asystole of over 3 s. SA node weakness (tachybradycardia syndrome) was diagnosed. An ECS was implanted.

In 2017, the patient had elevated BP (up to 200/110 mm Hg); losartan 25 mg daily was prescribed (the patient does not tolerate angiotensin converting enzyme inhibitors due to cough). June 2018: dizziness, speech disorder (dysarthria), progressing neurological symptoms — motor aphasia and moderate right-side hemiparesis. Brain CT did not show any focal lesions in the brain substance; an area of bilateral ischaemia was observed during follow-up; an ischaemic stroke was diagnosed in the vertebrobasilar system and left medial cerebral artery system. Brain CT in 2020 showed cystogliotic changes in cerebellar hemispheres and left fronto-temporal lobe. Anticoagulant therapy was recommended.

In June 2023, emergency ECS operation was reported: flat battery, broken atrial electrode. A two-chamber ECS BIOTRONIK in DDD-60 mode was re-implanted.

In September 2023, when the patient was 40 years old, she visited a cardiologist, complaining of irregular heart beat, burning pain on the left side of her chest when BP elevates to 150/100 mm Hg without any exercise stress; the episodes were managed with nitroglycerine or resolved on their own within 5 minutes. On physical examination, the overall condition was satisfactory. She is a wheel-chair user, can transfer herself to the bedside toilet and eat without assistance (Fig. 5). Skin and visible mucosa: pale, physiologically wet.

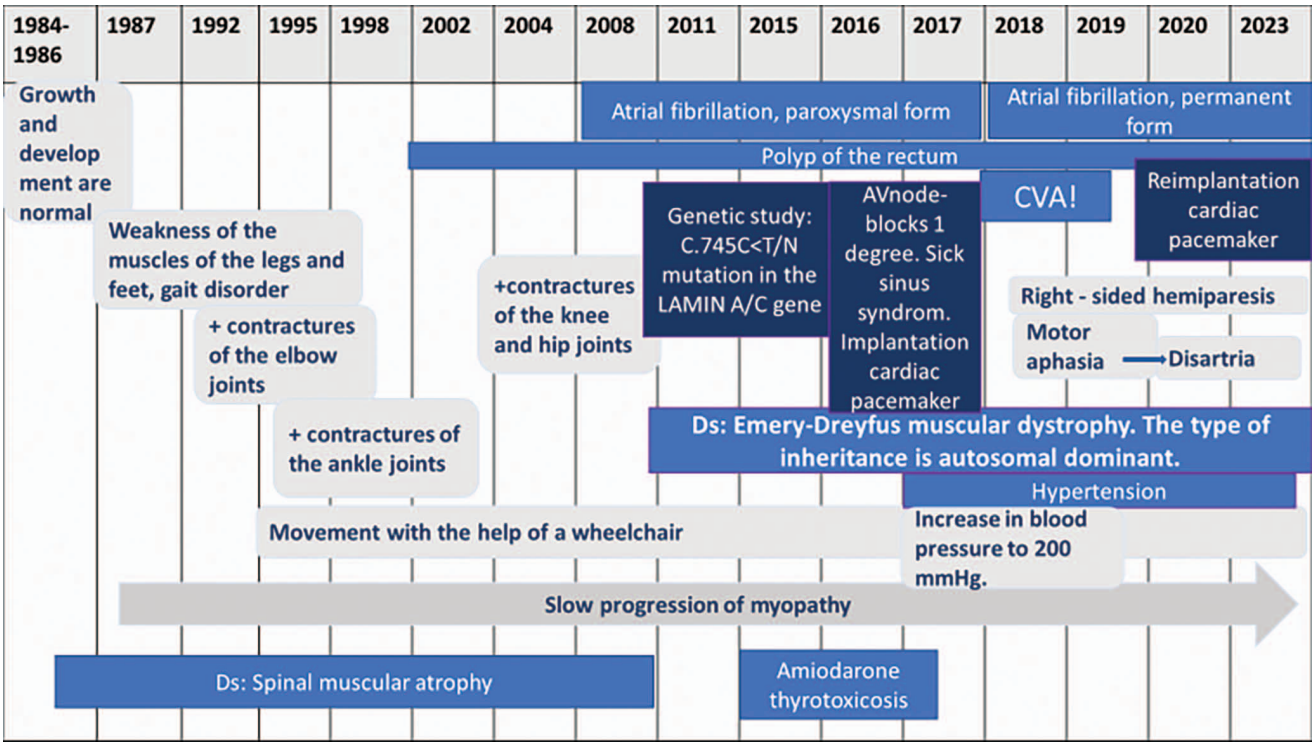

Figure 4. *Patient's anamnesis*

Body mass index: 11 kg/m^2. Neurologically: mildly flattened nasolabial fold on the right side, loss of hearing on the right, moderate dysarthria with tongue muscle atrophy. Quadriparesis with marked hypotrophy of pelvic and peroneal muscles, shoulder girdle muscles (winged shoulder blades) and muscles of proximal section of the upper and lower limbs. Diminished strength in proximal sections of her arms to 3 points, right hand — to 3 points, left hand — to 4 points, proximal and distal muscles of legs — to 3 points, with abnormal talipes varus. Elbow flexion contractures — to 110, right knee contractures — to 90, left knee contractures — to 140. Tendon reflexes are triggered by biceps on both sides, all other — by torpid. Rankin scale: 4 points. Breathing is unaided, clear, auscultatory weaker in the lower sections of the lungs on both sides. Oxygen saturation is 98 %. Region of the heart: visually unremarkable. Auscultation findings: muffled heart tones, irregular rhythm, systolic murmur in the tricuspid valve plane extending to the right axillary space and aggravating on inhalation. HR is 69 bpm, without pulse deficit. Blood pressure: 115/65 mm Hg. Abdomen is soft, painless, symmetric and engaged in respiration. Bowel movements are regular, unremarkable. Urination is unaided. No dysuria

Figure 5. *Patient's photo 40 years old (All materials are posted with the patient's consent)*

Blood biochemistry is remarkable for low-density lipoprotein levels of 2.3 mmol/L, which is outside the target range with a very high risk of CVCs in this patient (< 1.4 mmol/L). Total creatine phosphokinase level of 27 U/L is within the reference range, which is not exceptional for patients with EDMD (normal range: < 165 U/L). NTproBNP: 145 pg/mL (normal range: < 125 pg/mL, in CCF: < 300 pg/mL).

ECG shows AV rhythm, from 3rd complex — ECS rhythm; HR: 69 bpm, changes in the myocardium in the lower wall of left ventricle (Fig. 6).

EchoCG results for the period from 2017 to 2023 (Table 2) show reduced left ventricle volume, enlarged atria, higher systolic pressure in pulmonary artery, progressing tricuspid regurgitation as a result of impaired coaptation of the leaflets because of ECS (Fig. 7a, 7b).

Taking into account the complaints, past history, clinical presentation, instrumental and clinical test results, the following diagnosis can be made in this patient:

Primary disease: Progressing Emery — Dreifuss muscular dystrophy, autosomal dominant mode of inheritance; genetic testing dated 2011: mutated c.745C> T in gene LMNA, associated with LMNA-CMP.

Comorbidity: Controlled grade 3 arterial hypertension, very high risk of CVCs. Type IIB dyslipidaemia.

Complications: 1. SA node weakness (tachybradycardia syndrome). Grade 1 AV block. Permanent ECS from 2016, ECS BIOTRONIK reimplanted in June 2023 in DDD-60 mode.

2. Steady atrial fibrillation. EHRA IIA. CHA2DS2-VASC 4 points. HAS-BLED: 3 points.

3. Sequellae of past ischaemic ACVA in the vertebrobasilar system and left medial cerebral artery system in 2018; cardioembolic pathogenetic variant.

Using MOGES classification, this LMNA-CMP variant can be presented as follows [26]:

$$\mathbf{M}_{\text{ND[AF, AVB]}}\mathbf{O}_{\text{HM}}\mathbf{G}_{\text{AD}}\mathbf{E}_{\text{G LMNAc.745C<T/N}}\mathbf{S}_{\text{A-I.}}$$

MORAL-STAGE classification [52]:

$$\mathrm{M}_{\text{ND[AVB, AF]}}\mathrm{O}_{\text{H+M}}\mathrm{R}_{\text{LVTA(SCD) — 11,9 %, HF — 3.9 %-1 y.o.; 10.2 % — 3 y.o.}}$$
$$\mathrm{A}_{27}\mathrm{L}_{1}\,\mathrm{S}_{1\text{-}1}\mathrm{T}_{\text{S[AF+PM]}}\,\mathrm{A}_{\text{AF+AVB}}\mathrm{G}_{\text{AD}}\mathrm{E}_{\text{G LMNAc•745C<T/N}}$$

This patient faces a high risk of CCF: 3.9 % within 1 year, 10.2 % within 3 years. A 5-year risk of life-threatening ventricular tachyarrhythmias is 12.6 %.

The patient is recommended to continue antihypertensive therapy (losartan 50 mg daily), anticoagulant therapy (apixaban 2.5 mg twice daily). Ivabradine 5 mg was replaced with nebivolol 2.5 mg daily. Cholesterol-lowering therapy (pitavastatin 4 mg daily) was added.

Thus, the patient has the symptom triad typical for EDMD. A thorough past history evaluation and physical examination showed slowly progressing symptoms of muscle weakness and hypotrophy, early joint contractures, as well as rhythm and conduction abnormalities.

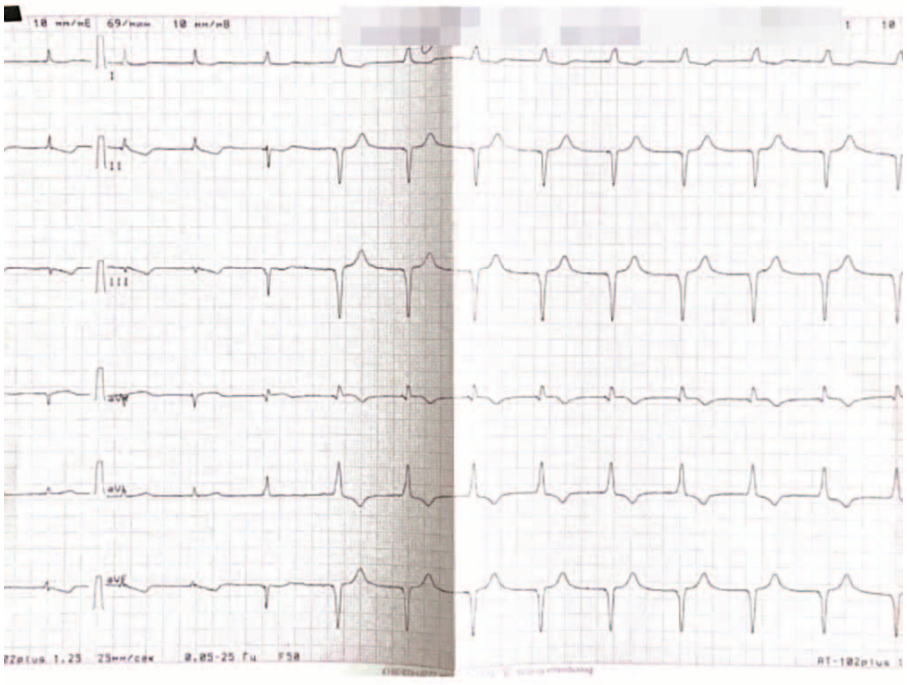

Figure 6. *ECG from September 2023*

Table 2. *Echocardiography parameters from 2017 to 2023*

Echo parameter	2017	2020	2023
IVSTd, cm	0.7	0.8	0.55
LV PWTd, cm	1.0	0.8	0.55
LV EDV, ml	79	-	46
LV ESV, ml	32	-	15
LV EF, %	60	69	66
LV ESD, cm	3.8	2.1	2.51
LV EDD, cm	4.2	3.6	4.59
RA, cm RA V, ml	3.9x3.6 33	4.0x3.5 44	4.54x4.79 59
LA, cm LA V, ml	3.3 38	3.6 40	3.75 57
RV EDD, cm	2.5	2.5	2.37
PASP, mm Hg	28	33	39
Doppler ECHO	MR I TR II PR I	MR I TR II PR I	MR I TR III PR I

Note: IVSTd — thickness of the interventricular septum in the diastole; LV — left ventricle, PWTd — thickness of the posterior wall in the diastole; EDV — end-diastolic volume; ESV — end-systolic volume ; EF — ejection fraction; ESD — end-systolic dimension; EDD — end-diastolic dimension; RA — right atrium; LA — left atrium; V — volume; RV — right ventricle; PASP — systolic pressure of the pulmonary artery; MR — mitral regurgitation, TR — tricuspid regurgitation, PR — pulmonary regurgitation

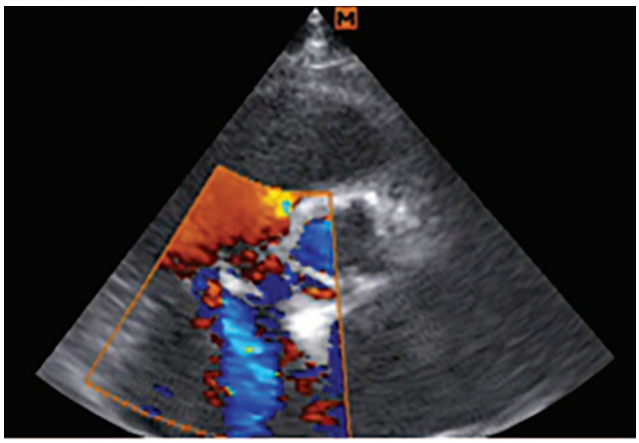

Figure 7a. *Parasternal short axis view. Color Doppler mapping mode. Tricuspid regurgitation (Blue flow)*

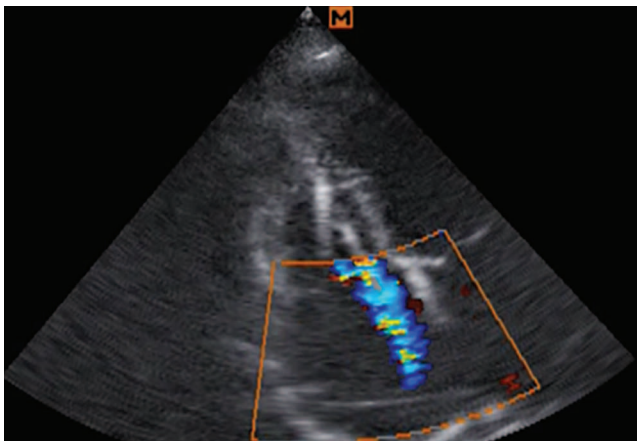

Figure 7b. *Apical four-chamber view. Color Doppler mapping mode. Tricuspid regurgitation (Blue flow)*

Therefore, a genetical cardioneurological disease was suspected; genetical testing was performed, the results of which enabled us to make the final diagnosis of EDMD with resulting LMNA-CMP.

Conclusion

Type 2 Emery — Dreifuss muscular dystrophy and other laminopathies are rare conditions; their common sign is *LMNA* gene mutation with similar phenotypes of cardiac involvement — LMNA-CMP.

A case study is described, and the clinical course of the disease is presented; CMP is defined and classified according to the latest recommendations of the European Society of Cardiology, MOGES, MORALSTAGE; risks of CCF and SCD for this patient were calculated.

Despite an inadequate level of knowledge of rare genetic conditions, patient management should take into account generally accepted strategies of CVC prevention, i.e. timely anticoagulant therapy in AFib to prevent TEC, taking into account high risks of conduction abnormalities, LTVT, SCD; early use of ECS/ICD/CRT should be considered to preserve the quality of life and improve prognosis. Management of patients with EDMD and LMNA-CMP requires a multidisciplinary team of specialists: neurologist, cardiologist, arrhythmia and rehabilitation specialists, GP, orthopaedist, genetic specialist, etc.

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Comments from the patient

I was born in Penza; I moved to Moscow when I was 23 years old and have been living there for 15 years. I attended the Penza Branch of the International Independent University of Environmental and Political Sciences to become a psychologist, but then I did not pursue my profession. At one point, I realised that I did not want to hear complaints of absolutely healthy and successful people. I moved beyond and in 2016 was qualified as a stylist. This year, I've learnt the basics of a profession, which gains popularity day by day — SMM specialist. I also organised concerts in child care homes on my own. Later it became my profession, and I was a project manager in a charitable trust for 15 years.

I've been a wheel-chair user since the age of 11. I have a genetic condition — muscle dystrophy, but it has never prevented me from communicating with people. When a child, I was on friendly terms with all children around me. We used to play together, sneak to nursery to get apples, and ride on a merry-go-rounds. We had a happy childhood!

I could not accept the wheel-chair and myself in it for over a year, although my transition to the wheel-chair was gradual. Some time later, I realised that I had no choice. Even those in a wheel-chair can have an interesting and happy life.

To those who have never been in a wheel-chair, I would like to remind: we are not different! We just need more comfort. We are happy when you do not take our parking spaces, when you do not step on the toilet seats in accessible toilets.

If you see someone in a wheel-chair, do not be afraid to ask if they need help. Do not stop children when they take interest in disabled people. Just be ready to explain to your child that we move around differently. Be more sensitive and do not be afraid to show your love.