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CONTENTS

ORIGINAL STUDY ARTICLES

S.M. Komissarova, N.N. Chakova, N.M. Rineiska, S.S. Niyazova, T.V. Dolmatovich, V.Ch. Barsukevich, L.I. Plashchinskaya
Unexplained cardiac arrest (idiopathic ventricular fibrillation): clinical and genetic characteristics 5

N.V. Bukvalnaya, L.V. Yakubova, A.V. Kapytski, L.V. Kezhun, O.V. Gorchakova, D.G. Karnialiuk, E.Yu. Charnetskaya, V.A. Snezhitskiy
Genetic markers and traditional risk factors in predicting atrial fibrillation in patients with arterial hypertension, focus on the renin-angiotensin-aldosterone system genes 19

CLINICAL CASE

Yu.N. Grishkin, V.Yu. Zimina, A.A. Babayan, P.O. Karchikian, T.D. Butaev, O.V. Grigorieva
An arrhythmic variant of the manifestation of paraneoplastic Loeffler endomyocarditis. Clinical case 29

N.S. Tretyakova, S.A. Boldueva, I.A. Leonova, O.S. Shvetsova, L.S. Evdokimova
Clinical case of successful treatment of focal ventricular arrhythmia in a patient with arrhythmogenic mitral valve prolapse 41

СОДЕРЖАНИЕ

ОРИГИНАЛЬНЫЕ ИССЛЕДОВАНИЯ

С.М. Комиссарова, Н.Н. Чакова, Н.М. Ринейская, С.С. Ниязова, Т.В. Долматович, В.Ч. Барсукевич, Л.И. Плащинская
Необъяснимая остановка сердца (идиопатическая фибрилляция желудочков): клиническая и генетическая характеристика 5

Н.В. Буквальная, Л.В. Якубова, А.В. Копыцкий, Л.В. Кежун, О.В. Горчакова, Д.Г. Корнелюк, Е.Ю. Чернецкая, В.А. Снежицкий
Генетические маркеры и традиционные факторы риска в прогнозировании фибрилляции предсердий у пациентов с артериальной гипертензией, фокус на гены ренин-ангиотензин-альдостероновой системы 19

КЛИНИЧЕСКИЙ СЛУЧАЙ

Ю.Н. Гришкин, В.Ю. Зимина, А.А. Бабаян, П.О. Карчикьян, Т.Д. Бутаев, О.В. Григорьева
Аритмический вариант манифестации паранеопластического эндомиокардита Леффлера. Клинический случай 29

Н.С. Третьякова, С.А. Болдуева, И.А. Леонова, О.С. Швецова, Л.С. Евдокимова
Клинический случай успешного лечения фокусной желудочковой аритмии у пациентки с аритмогенным пролапсом митрального клапана 41

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Unexplained cardiac arrest (idiopathic ventricular fibrillation): clinical and genetic characteristics

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ABSTRACT

AIM: The study was to evaluate the clinical and genetic characteristics of inherited arrhythmias in patients who survived unexplained cardiac arrest.

MATERIALS AND METHODS: 20 patients (10 male and 10 female) aged 15 to 55 years (median age 36 [28; 44] years) with documented VT/VF on ECG were observed for 3 years. The clinical and instrumental study included registration of 12-lead ECG, 24-hour Holter ECG, genealogical history collection and family history of sudden cardiac death with ECG assessment of all family members, transthoracic echocardiography, 2D Speckle Tracking echocardiography and cardiac magnetic resonance imaging to exclude structural myocardial changes. High-throughput sequencing (NGS) was utilized to search for mutations in genes linked to the onset of channelopathies and other inherited rhythm disorders.

RESULTS: In 4 (20%) of the 20 probands included in the study, likely pathogenic variants were identified (pathogenicity class IV), and in 7 (35%) patients, variants with unknown clinical significance (pathogenicity class III) in 10 genes associated with channelopathies (*KCNQ1*, *KCNH2*, *SCN5A*, *AKAP9*, *ANK2*, *SCN10*A, *RYR2)* and cardiomyopathies (*MYH7*, *JPH2*, *RBM20*). Several genetic variants were found in 3 cases. No significant genetic changes were detected in 9 (45 %) probands. The clinical diagnosis was established during the follow-up period and was verified due to the genetic testing in 5 (25 %) patients. From their ECGs, a prolonged *QTc* > 460 ms was found in 1 patient, Brugada pattern in 2 individuals, and a shortening of *QTc* up to 323 ms in 1 proband. Subclinical structural changes associated with cardiomyopathies were revealed in 2 patients. In 15 (75 %) patients, it was unfeasible to establish a distinct clinical phenotype. In 6 (30 %) probands, the diagnosis was clarified due to detected genetic variants.

CONCLUSION: Clinical manifestations and diverse genetic variants have been studied in patients who have survived unexplained cardiac arrest. In the course of genotyping patients who suffered unexplained cardiac arrest, genetic changes associated with LQTS were detected in 30 % of cases, while the *QTc* in most cases did not exceed 440 ms, which makes it difficult to establish a diagnosis at an early stage before the development of life-threatening arrhythmic events. The data from our study confirm the idea that in patients with idiopathic ventricular fibrillation, who have suffered unexplained cardiac arrest, cardiac channelopathy or subclinical manifestations of cardiomyopathy are commonly the cause. This phenomenon imposes a need for genetic testing in this category of patients.

Keywords: unexplained cardiac arrest; idiopathic ventricular fibrillation; genotypic and phenotypic diversity.

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Необъяснимая остановка сердца (идиопатическая фибрилляция желудочков): клиническая и генетическая характеристика

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АННОТАЦИЯ

Цель исследования — оценить клиническую и генетическую характеристики наследственных аритмий у пациентов, переживших необъяснимую остановку сердца.

Материалы и методы. Обследовано 20 пациентов (10 мужского и 10 женского пола) в возрасте в возрасте от 15 до 55 лет (медиана возраста 36 [28; 44] лет) с документированной желудочковой тахикардией / фибрилляцией желудочков на электрокардиограмме, наблюдаемых в течение 3 лет. Клинико-инструментальное исследование включало: регистрацию электрокардиограмм в 12 отведениях, холтеровское мониторирование, сбор генеалогического анамнеза с оценкой электрокардиограмм всех членов семьи с выявлением случаев внезапной сердечной смерти в семье или наличия семейной формы заболевания, трансторакальную и 2D Speckle Tracking эхокардиографию и магнитно-резонансную томографию сердца для исключения структурных изменений миокарда. Поиск мутаций в кодирующих последовательностях генов, ассоциированных с развитием каналопатий и других наследственных нарушений ритма, проводили методом высокопроизводительного секвенирования.

Результаты. У 4 (20 %) из 20 включенных в исследование пробандов выявлены вероятно патогенные варианты (IV класс патогенности), у 7 (35 %) пациентов — замены с неизвестной клинической значимостью (III класс патогенности) в 10 генах, ассоциированных с каналопатиями (*KCNQ1*, *KCNH2*, *SCN5A*, *AKAP9*, *ANK2*, *SCN10A*, *RYR2)* и кардиомиопатиями (*MYH7*, *JPH2*, *RBM20*). Сочетание нескольких генетических вариантов обнаружено в 3 случаях. У 9 (45 %) из 20 пробандов значимых генетических изменений не выявлено. Клинический диагноз был установлен в период последующего наблюдения при комплексном обследовании и верифицирован в результате генетического обследования у 5 (25 %) пациентов. При анализе серии электрокардиограмм на одной из них выявлено удлинение интервала *QTc* > 460 мс; у 2 — паттерн Бругада; еще у 1 — укорочение интервала *QTc* до 323 мс. У 2 пациентов выявлены субклинические структурные изменения, ассоциированные с кардиомиопатиями. У 15 (75 %) пациентов не удалось установить явного клинического фенотипа. У 6 (30 %) из них диагноз был уточнен благодаря обнаруженным генетическим вариантам.

Заключение. Изучены клинические проявления и различные генетические варианты у пациентов, переживших необъяснимую остановку сердца. При генотипировании пациентов, перенесших необъяснимую остановку сердца, в 30 % случаев обнаруживали генетические изменения, ассоциированные с LQTS, при этом интервал *QTc* в большинстве случаев не превышал 440 мс, в связи с чем установление диагноза на ранней стадии до развития жизнеугрожающего аритмического события затруднено. Данные нашего исследования подтверждают идею о том, что у пациентов с идиопатической фибрилляцией желудочков, перенесших необъяснимую остановку сердца, в основе заболевания довольно часто лежат сердечная каналопатия или субклинические проявления кардиомиопатии, что диктует необходимость проведения генетического тестирования у этой категории пациентов.

Ключевые слова: необъяснимая остановка сердца; идиопатическая фибрилляция желудочков; генотипическое и фенотипическое разнообразие.

Как цитировать

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INTRODUCTION

Sudden cardiac death (SCD) is the most common cause of mortality from cardiovascular diseases. Annually, 1–3 individuals per 100,000 people aged <35 years suddenly die [1, 2]. Studies have reveald that the frequent underlying cause of sudden cardiac arrest is inherited cardiac channelopathies [3, 4]. Autopsy findings of cardiomyopathy can be confirmed by postmortem genetic testing [5]. However, 30–40% of SCD cases in young adults remain unexplained [4, 6, 7]. Patients who survive cardiac arrest after administered cardiopulmonary resuscitation (CPR) may have genetic diseases for which genetic testing is mandatory. Such patients should undergo a comprehensive clinical evaluation focused on identifying the causative disease. If no aetiology is found, the patient is diagnosed with unexplained cardiac arrest (UCA) or idiopathic ventricular fibrillation (IVF). IVF is defined as UCA in a resuscitated patient showing no abnormalities on electrocardiogram (ECG) and in whom known cardiac, respiratory, metabolic, and toxicologic causes have been excluded by clinical evaluation [3, 4]. Studies have shown that IVF accounts for 5–7% of all out-of-hospital cardiac arrests [8].

According to the current European Heart Rhythm Association/Heart Rhythm Society/Asia Pacific Heart Rhythm Society/Latin American Heart Rhythm Society expert consensus statement on the state of genetic testing for cardiac diseases (EHRA/HRS/APHRS/LAHRS-2022) [9], genetic testing for diagnostically significant variants is recommended in UCA survivors in addition to a comprehensive clinical evaluation, and if detected, cascade screening of relatives is warranted [10].

In previous studies concerning the diagnostic use of postmortem genetic testing, a series of unexplained cardiac deaths in 26% of cases revealed the presence of allegedly pathogenic variants in genes associated with major channelopathies, including catecholaminergic polymorphic ventricular tachycardia (CPVT) (*RYR2* gene), long *QT* syndrome (LQTS) types 1–3 (*KCNQ1, KCNH2*, and *SCN5A* genes), and Brugada syndrome type 1 (*SCN5A* gene) [7]. Genetic screening of autopsy material from 302 individuals who died of sudden arrhythmic death syndrome was recently conducted. According to the 2015 American College of Medical Genetics and Genomics (ACMG) criteria, pathogenic and likely pathogenic variants in genes associated with channelopathies were identified in 11% of cases [11]. Additionally, pathogenic variants were identified in 2% of cases in genes associated with cardiomyopathies, indicating a structural cause of UCA that may have not been detected. The diagnostic yield increased by an average of 30% with the implementation of molecular genetic screening and clinical examination of family members [10, 11]. Genetic testing of UCA survivors using extended panels revealed the number of channelopathies and cardiomyopathies with an alleged pathogenic variant ranging from 3% to 27% [8, 12, 13].

The present study analyzed a cohort of patients with UCA caused by IVF who were successfully resuscitated and underwent implantation of cardioverter-defibrillator (ICD). Genetic alterations were assessed in these patients.

This study aimed to evaluate the clinical and genetic characterization of inherited arrhythmias in patients who survived UCA.

MATERIALS AND METHODS

Twenty patients (10 men, 10 women) aged 15–55 years with documented ventricular tachycardia (VT)/ventricular fibrillation (VF) on ECG were enrolled consecutively. The median follow-up period was 3 years.

Patients who had UCA with documented VT or VF requiring cardioversion or defibrillation, no left ventricular (LV) dysfunction (LV ejection fraction ⩾50%), and intact coronary arteries (no coronary stenosis >50%) were included. In contrast, patients with known causes of cardiac arrest ($n = 5$), including ECG diagnosis of LQTS (resting *QTc* >460 ms in men and 480 ms in women) or Brugada syndrome, hypertrophic cardiomyopathy, marked hypokalemia, and drug overdose, were excluded. Genetic testing, which was approved by the local ethics committee, was performed on all the study patients (minutes no. 2 of the meeting of the Bioethics Committee of the Institute of Genetics and Cytology of the National Academy of Sciences of Belarus, dated June 8, 2021). All patients signed a voluntary informed consent to participate in the study.

Clinical and instrumental studies included a resting 12-lead ECG using the Intercard-3 recorder (Republic of Belarus), transthoracic echocardiography (TTE) using the IE-33 ultrasound system (Philips, USA), X-ray selective coronary angiography using Innova 3100 (General Electric, USA) and Siemens Artis Zee Cath/Angio System (Siemens, USA), or coronary CT scan (Siemens Somatom Force, Germany). Patients who met the enrollment criteria underwent further testing, including 24-hour Holter monitoring using Philips Zimed (Austria) and Oxford Medilog AR12 (UK) recorders, 2D Speckle Tracking TTE using Vivid 7 premium cardiac ultrasound system (General Electric, USA), and cardiac magnetic resonance imaging (MRI) using Magnetom Aera 1.5 T tomograph (Siemens, Germany) according to recent recommendations.

Mutations in the coding sequences of genes associated with channelopathies and other inherited cardiac arrhythmias were evaluated with high-throughput next-generation sequencing (NGS) using a MiSeq Gene Analyzer (Illumina, USA). Samples were prepared with the TruSight Cardio Sequencing Kit (Illumina, USA), which contains 174 genes associated with inherited cardiovascular diseases. Annotation of the sequencing results was conducted using the ANNOVAR software [14]. The clinical significance of new and previously

described genetic variants was evaluated according to the 2015 ACMG recommendations. [15]. The following factors were considered: the prevalence of the identified genetic variant in large population samples (Genome Aggregation Database [GnomAD]), localization in the gene and variant type, prediction of pathogenicity *in silico*, assessment of pathogenicity status in genetic databases (ClinVar, HGMD) and in peer-reviewed literature, availability of functional studies, and analysis of cascade screening data to elucidate variant segregation with disease within a family. Genetic variants classified as pathogenic (class V) and likely pathogenic (class IV) were considered diagnostically significant. Additionally, variants of uncertain significance (VUS; class III), which were predicted to be pathogenic *in silico* and whose frequency of occurrence in population databases (GnomaD) did not exceed 0.01%, were analyzed.

Statistical analysis was conducted using the StatSoft Statistica version 12.0 package and Microsoft Excel 2021. The quantitative data were represented by the median and quartiles in the form of *Me* [*LQ; UQ*], whereas the qualitative data were described by absolute values and percentages (*n* [%]).

RESULTS

Overall, 20 patients (10 women, 10 men; median age: 36 [28; 44] years) who had UCA caused by IVF and underwent resuscitation and ICD implantation were studied. Among the patients, 16 (80%) had a history of syncope. Moreover, 4 (20%) patients had close relatives with SCD (Table 1). The patients' clinical and instrumental characteristics are presented in Table 2.

Genotyping by NGS revealed likely pathogenic variants in 4 (20%) patients (Table 3). In 7 (35%) probands, variants of unknown clinical significance (pathogenicity class III) were detected in 10 genes associated with channelopathies (*KCNQ1, KCNH2, SCN5A, AKAP9, ANK2, SCN10A*, and *RYR2*) and cardiomyopathies (*MYH7, JPH2*, and *RBM20*). A combination of several genetic variants was found in three patients. No significant genetic changes were determined in 9 (45%) of 20 probands. Clinical diagnosis was established during the follow-up period by comprehensive examination and confirmed by genetic testing in 5 (25%) patients (codes 873c, 15m, 732, 799, and 642). Serial ECGs showed *QTc* interval prolongation >480 ms in one patient (code 873c), Brugada pattern in two patients (codes 732 and 799), and *QTc* interval shortening up to 323 ms in one patient (code 15m). Subclinical structural changes associated with cardiomyopathies were identified in two patients (codes 816 and 868c). In 15 (75%) patients, no clear clinical phenotype was established (codes 829, 586, 543, 642c, 590, 868c, 644, 647, 629, 612, 729, 805, 574, 648c, and 782). In 6 (30%) patients (codes 829, 586, 543, 642c, 590, and 868c), the diagnosis was clarified using the genetic variants detected.

LQTS-related genetic alterations were prevalent among patients with UCA caused by VF, occurring in 30% of cases. Proband 873c (female, 48 years old) exhibited *QTc* prolongation caused by a variant in the *KCNH2* gene (Fig. 1). The disease manifested at age 48 years with cardiac arrest, which was treated with resuscitation and subsequent ICD implantation. A series of ECGs obtained over the past year demonstrated no alterations in T wave morphology or *QTc* prolongation (420–440 ms). An ECG performed a year ago exhibited *QTc* prolongation of up to 482 ms. The patient had been suffering from syncope and presyncope for approximately 3 years. Based on the genotyping data, LQTS type 2 was diagnosed.

VUS in exons 15 and 38 of the *ANK2* gene, which encodes the adaptor protein ankyrin-B, were identified in two unrelated male probands (codes 543 and 586).

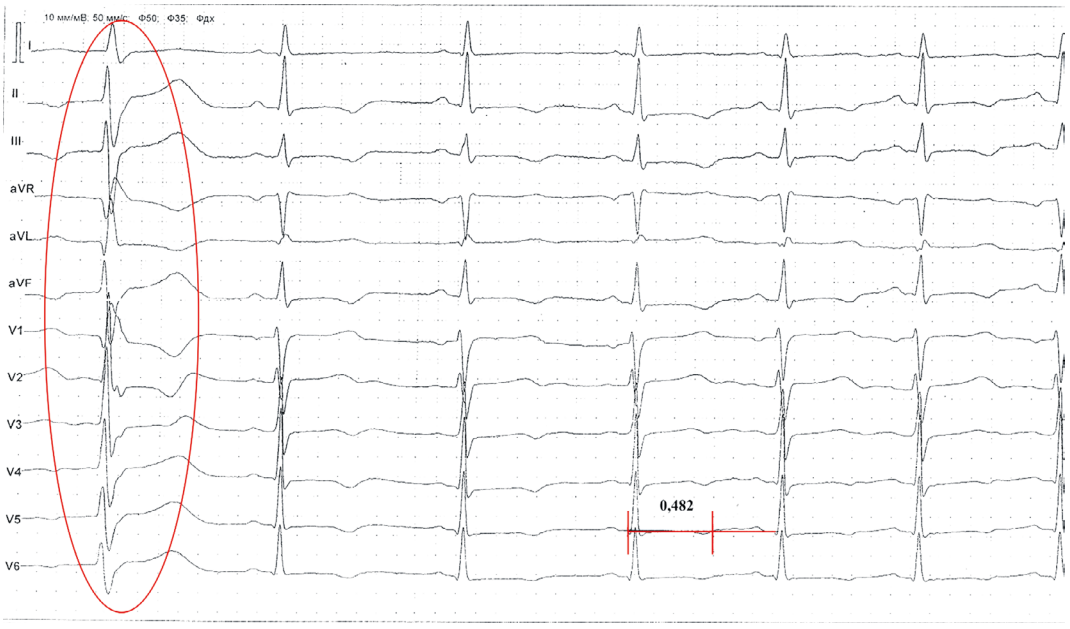

Fig. 1. 12-lead ECG of proband 873c. Prolonged QTc interval — 482 ms, ventricular premature beat (red ellipse)

Table 1. Clinical and genetic characteristics of patients with idiopathic ventricular fibrillation

Patient code	Age	Sex	Family history of SCD	History of syncope	*QTc* max	Gene (variant class)	Clarified diagnosis	Events/outcomes
873c	48	female	–	+	530	*KCNH2* (III–IV)	LQTS2	VF, CPR, ICD
829	44	female	–	+	380	*AKAP9* (III)	LQTS11	VF, CPR, ICD
586	33	male	–	+	445	*ANK2* (III)	LQTS4	VF, CPR, ICD
543	45	male	–	+	375	*ANK2* (III)	LQTS4	Recurrent VT/VF, ICD, electrical storms
15м	29	male	–	–	323	*KCNQ1* (III)	SQTS	VF, CPR, ICD
732	55	female	–	+	430	*SCN10A* (III)	BrS	VF, ICD
799	41	male	+	+	420	*SCN5A* (V) *JUP* (III)	BrS	VF, ICD
642c	15	male	–	+	450	*RYR2* (IV–V)	CPVT	VT/VF, CPR, ICD
590	21	male	–	–	374	*CACNA1C* (III)	IVF	VF, CPR, ICD
816	19	male	+	–	380	*RBM20* (IV) *MYH7* (III)	NDLVC	VF/EC
868c	36	female	–	+	410	*KCNH5* (III) *JPH2* (III)	IVF	VF, EC, ICD
644	46	female	–	+	460	not detected	IVF	VT/VF, ICD
647	46	male	–	+	477	not detected	IVF	VT/VF, ICD
629	40	female	–	+	478	not detected	IVF	VF, CPR, ICD
612	16	male	–	+	380	not detected	IVF	VF, CPR, ICD
729	44	female	–	+	405	not detected	IVF	VF, CPR, ICD
805	23	female	–	+	340	not detected	IVF	VF, CPR, ICD
574	30	female	+	+	450	not detected	IVF	VF, CPR, ICD
648c	36	female	+	+	448	not detected	IVF	VF, CPR, ICD
782	30	male	–	–	420	not detected	IVF	VF, CPR, ICD

Note: SCD — sudden cardiac death; VF — ventricular fibrillation; CPR — cardiopulmonary resuscitation; ICD — implantable cardioverter-defibrillator; VT — ventricular tachycardia; EC — electrical cardioversion; LQTS — long *QT* syndrome; SQTS — short *QT* syndrome; CPVT — catecholaminergic polymorphic ventricular tachycardia; IVF — idiopathic ventricular fibrillation; NDLVC — non-dilated left ventricular cardiomyopathy; BrS — Brugada syndrome.

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Table 2. Clinical and instrumental characteristics of patients with unexplained cardiac arrest

Parameters	Group of patients with UCA (*n* = 20)
Clinical parameters	
Age at diagnosis, years, *Me* [*LQ*; *UQ*]	36 [28; 44]
Age of disease manifestation, years, *Me* [*LQ*; *UQ*]	35 [27; 41]
Gender, *n* (%)	
Female	10 (50)
Male	10 (50)
Family history of SCD, *n* (%)	4 (20)
Syncope, *n* (%)	16 (80)
Clinical phenotype, *n* (%)	
LQTS	4 (20)
SQTS	1 (5)
Brugada syndrome	2 (10)
CPVT	1 (5)
NDLVC	1 (5)
IVF	11 (55)
QTc max, *Me* [*LQ*; *UQ*]	420 [380; 450]
TTE parameters	
LV EF, %, *Me* [*LQ*; *UQ*]	58 [56; 63]
LAVI, mL/m^2,*Me* [*LQ*; *UQ*]	34 [30; 38]
LV EDD, mm, *Me* [*LQ*; *UQ*]	50 [48; 53]
LV ESD, mm, *Me* [*LQ*; *UQ*]	31 [30; 34]
LV EDV, mL, *Me* [*LQ*; *UQ*]	112 [106; 135]
LV ESV, mL, *Me* [*LQ*; *UQ*]	49 [36; 56]
PASP, mmHg, Me [LQ; UQ]	21 [20; 23]

Note: UCA — unexplained cardiac arrest; SCD — sudden cardiac death; LQTS — long *QT* syndrome; SQTS — short *QT* syndrome; CPVT — catecholaminergic polymorphic ventricular tachycardia; IVF — idiopathic ventricular fibrillation; NDLVC — non-dilated left ventricular cardiomyopathy; *QTc* — corrected *QT* interval; TTE — transthoracic echocardiography; LV EF — left ventricular ejection fraction; LAVI — left atrium volume index; LV EDD — left ventricular end-diastolic diameter; LV ESD — left ventricular end-systolic diameter; LV EDV — left ventricular end-diastolic volume; LV ESV — left ventricular end-systolic volume; PASP — pulmonary artery systolic pressure.

Both patients exhibited no aggravated family history and demonstrated *QTc* interval prolongation on ECG series (median *QTc*: 407.5 [375; 440] ms). Prior to the onset of VF, the patients experienced recurrent syncope requiring CPR and ICD implantation. Patient 543 (male, 43 years old) who had a p.Thr466Met substitution in the ANK2 gene developed polymorphic VT/VF controlled by an ICD multiple times during the 8-year follow-up, which led to ICD replacement 3 times. During the last 2 years, no recurrences of syncopal episodes and multiple ICD storms requiring CPR were noted. Considering the results of genotyping, the patients were diagnosed with IVF probably caused by mutations in the ankyrin gene.

In proband 829 (female, 44 years old) who showed a novel variant in the *AKAP9* gene, no family history of SCD and no *QT* interval prolongation on serial ECGs were recorded. The disease manifested at age 44 years with cardiac arrest caused by VF, which required CPR and ICD implantation. Frequent premature ventricular contractions and sustained and nonsustained paroxysms of VT were recorded during 24-hour Holter monitoring (Fig. 2). A comprehensive examination showed no structural myocardial abnormalities. Considering the genotyping data, VF was diagnosed due to the variant in the *AKAP9* gene. However, subsequent cascade screening of the proband's son (32 years old) and daughter (25 years old) using Sanger sequencing did not establish the pathogenic significance of the new variant, because both children were carriers of the same c.8747C>T substitution in the *AKAP9* gene, but had no ECG alterations and no other clinical manifestations. Owing to the incomplete penetrance of the disease and pathogenicity of the variant according to *in silico* prognostic predictors, regular follow-up with a cardiologist was recommended.

Cardiac arrest due to IVF and subsequent ICD implantation were recorded in four genotype-negative patients (codes 644, 647, 629, and 574) with borderline *QTc* values on ECG (median 465 [460; 477]). Moreover, two of the patients had a family history of SCD, indicating a hereditary nature of the disease (Table 1).

In 2 (10%) patients, the disease manifested with the development of IVF following CPR and ICD implantation; a Brugada pattern was detected on ECG at follow-up. Proband 799 (male, 41 years old) had a family history of SCD; his father died from SCD at age 28 years (Fig. 3). The proband experienced syncopal episodes unrelated to physical activity during the day and, eventually, cardiac arrest developed at night. ECG showed a spontaneous Brugada type 1 pattern. Hereinafter, no Brugada pattern was observed, and sinus rhythm with HR at 68 beats/min, *PQ* interval duration at 110 ms, *QTc* interval at 380 ms, and *QRS* at 120 ms was recorded. Genotyping revealed a likely pathogenic variant p.Glu48Lys in the *SCN5A* gene and an additional substitution in the *JUP* gene associated with arrhythmogenic right ventricular cardiomyopathy (ARVC).

Cardiac MRI showed no structural myocardial changes nor evidence of ARVC. Considering the genotyping data, Brugada syndrome was diagnosed. Cascade screening in the proband's younger brother (31 years old) and daughter (10 years old) revealed a variant in the *SCN5A* gene. Neither had a substitution in the *JUP* gene, herewith the daughter having syncopal episodes and the younger brother being asymptomatic.

Patient 732 (female, 55 years old, no family history of SCD) who was admitted to the intensive care unit with cardiac arrest had a recorded VF and was subsequently implanted with an ICD. ECG showed a Brugada type 1 pattern (Fig. 4). Genotyping revealed a p.Asp1739Val substitution in the *SCN10A* gene encoding a neuronal sodium channel (Nav1.8), which has been associated with Brugada syndrome in recent whole-genome association studies. Phenotypic similarities have been demonstrated between patients with a *SCN10A* gene variant and *SCN5A* gene variants, including family history, presence of syncope, and spontaneous ECG pattern [16].

In patient 642c (male, 15 years old), the disease manifested at age 15 years with the development of cardiac arrest caused by polymorphic VT/VF (Fig. 5). CPR was performed, and a ICD was implanted for secondary prevention of SCD. Genotyping revealed a pathogenic mutation, c.14876G > A (p.Arg4959Gln, rs794728811), in the *RYR2* gene. Based on these results, CPVT was diagnosed. The mother of the proband was found

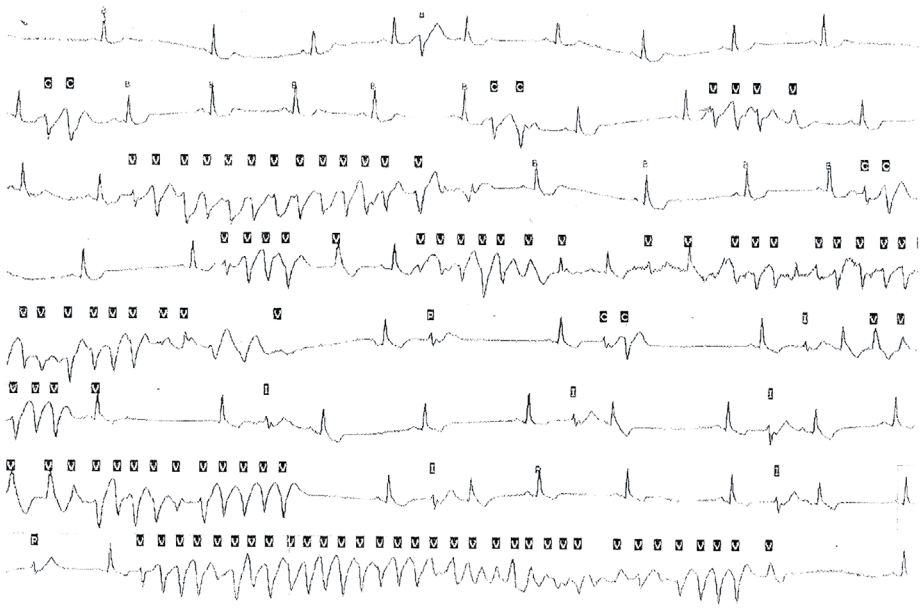

Fig. 2. 24-hour Holter ECG of patient 829. Ventricular premature beats and paroxysms of nonsustained ventricular tachycardia

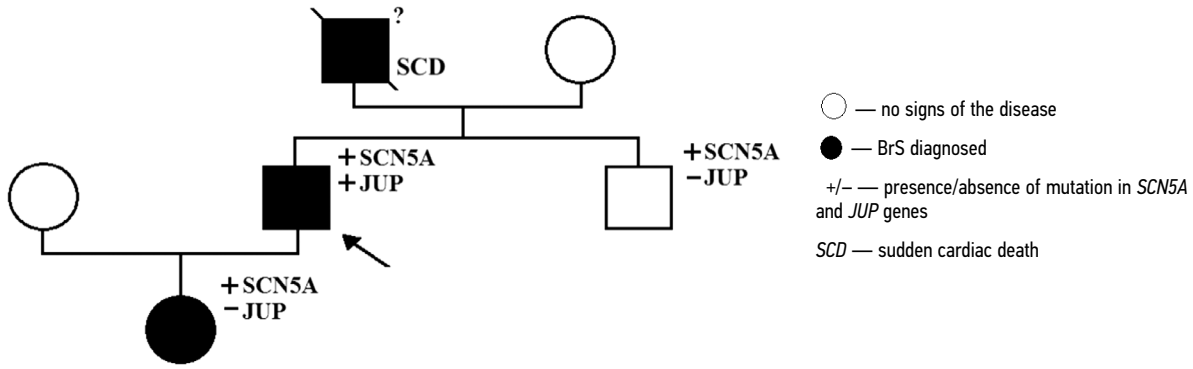

Fig. 3. Pedigree of the proband 799's family with mutations p.Glu48Lys in *SCN5A* gene and p.Ala143Thr in *JUP* gene. The proband is indicated by an arrow. Clinically affected individuals are indicated by the shaded symbols

Table 3. Genetic characteristics of variants in patients with idiopathic ventricular fibrillation

Patient code	Gene	Nucleotide substitution / Rs	Amino acid substitution	Variant class	MAF (GnomaD)
873c	*KCNH2*	c.2948C>T rs149955375	p.Thr983Ile	LP/VUS	0.00001983
829	*AKAP9*	c.8747C>T rs146648044	p.Thr2916Ile	VUS*	–
586	*ANK2*	c.9161C>G rs139007578	p.Ala3054Gly	VUS	0.00001363
543	*ANK2*	c.1397C>T rs786205722	p.Thr466Met	VUS	0.00005373
15м	*KCNQ1*	c.1831G>A rs147445322	p.Asp611Asn	VUS	0.000072
799	*SCN5A*	c.142G>A, rs199473048	p.Glu48Lys	LP	0.000039
	JUP	c.427G>A, rs375788626	p.Ala143Thr	VUS	0.00009858
732	*SCN10A*	c.5216 A>T, rs760863009	p.Asp1739Val	VUS	0.000014
642c	*RYR2*	c.14876G>A rs794728811	p.Arg4959Gln	P/LP	–
590	*CACNA1C*	c.5432_5433insCAACGCCAACATCAA rs765818401	p.S1811delinsSNANIN	VUS	0.000012
816	*MYH7*	c.4984C>T rs773977507	p.Arg1662Cys	VUS	0.000007955
	RBM20	c.2656-1G>A	splicing	LP*	–
868c	*JPH2*	c.1275C>A rs2145840509	p.Asp425Glu	VUS	–
	KCNA5	c.497A>C rs748629738	p.Asp166Ala	VUS	0.0001221

Note: * — new variant; P — pathogenic variant; LP — likely pathogenic; VUS — variants of uncertain significance; MAF — minor allele frequency.

to have the same mutation, which manifested clinically as presyncope and palpitations.

In patient 590 (male, 21 years old), a comprehensive clinical examination following cardiac arrest and resuscitation with subsequent ICD implantation revealed no structural abnormalities or ECG alterations. Genotyping identified a *CACNA1C* gene variant, which encodes the *L*-type calcium channel alpha subunit (CAV1.2). This variant is associated with channelopathies, namely, Timothy syndrome. However, no changes were detected on ECG, and no indications of syndactyly, cognitive impairment, facial dysmorphism, or other noncardiac characteristics suggestive of Timothy syndrome were observed.

Notably, variants in genes associated with the development of cardiomyopathy were detected in two patients with IVF. In patient 816 (male, 19 years old), who exhibited no myocardial structural abnormalities at the time of examination, variants in the *RBM20* and *MYH7* genes associated with various cardiomyopathies, including the dilated cardiomyopathy or non-dilated left ventricular cardiomyopathy (NDLVC) phenotype, were detected on TTE and cardiac MRI. The patient had no obvious clinical phenotype during VF. A family history of SCD was noted; his mother developed the disease at age 33 years. At 2-year follow-up, 2D-Strain TTE showed a moderate decrease in global longitudinal strain (–13.6%) (Fig. 6), with no LV dilatation, confirming cardiomyopathy. Thus, the diagnosis of IVF was changed to NDLVC. In patient 868c (female, 36 years old), in the absence of myocardial structural abnormalities, variants in *JPH2* genes associated with cardiomyopathies and in *KCNA5* associated with familial atrial fibrillation were detected on TTE and cardiac MRI. No alterations of T wave morphology or prolonged *QTc* interval (*QTc*: 420–440 ms) were observed on ECG. No atrial fibrillation was determined in the patient's medical history or during 24-hour Holter monitoring. Moreover, no evidence of cardiomyopathy or cardiac channelopathy was found in the patient's family history. Currently, subclinical structural myocardial abnormalities are suspected in the patient, and further follow-up is required to confirm the diagnosis.

In a group of 20 patients with UCA and VF, the clinical phenotype was linked to genetic variants in 11 (55%) patients,

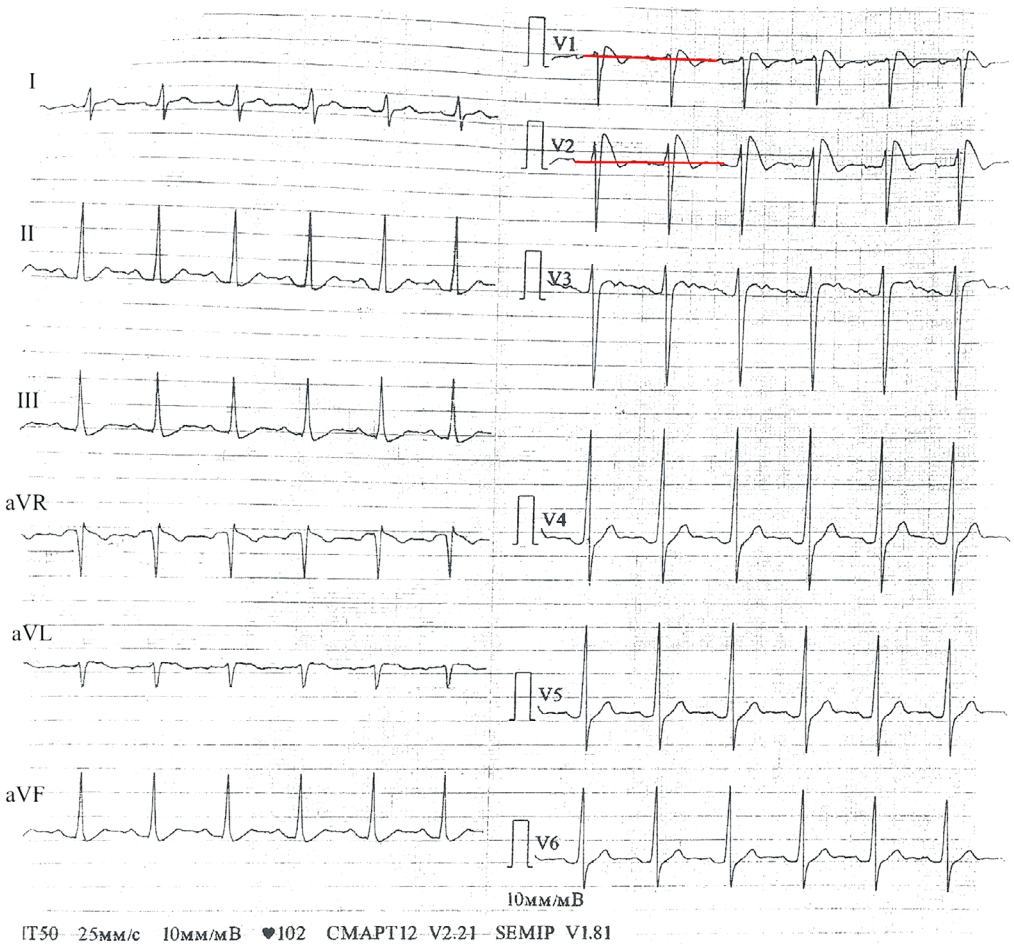

Fig. 4. 12-lead ECG of patient 732 with Brugada pattern type 1 ("coved"), showing a "vaulted" ST elevation of more than 2 mm in V1–V2, followed by a negative T-wave

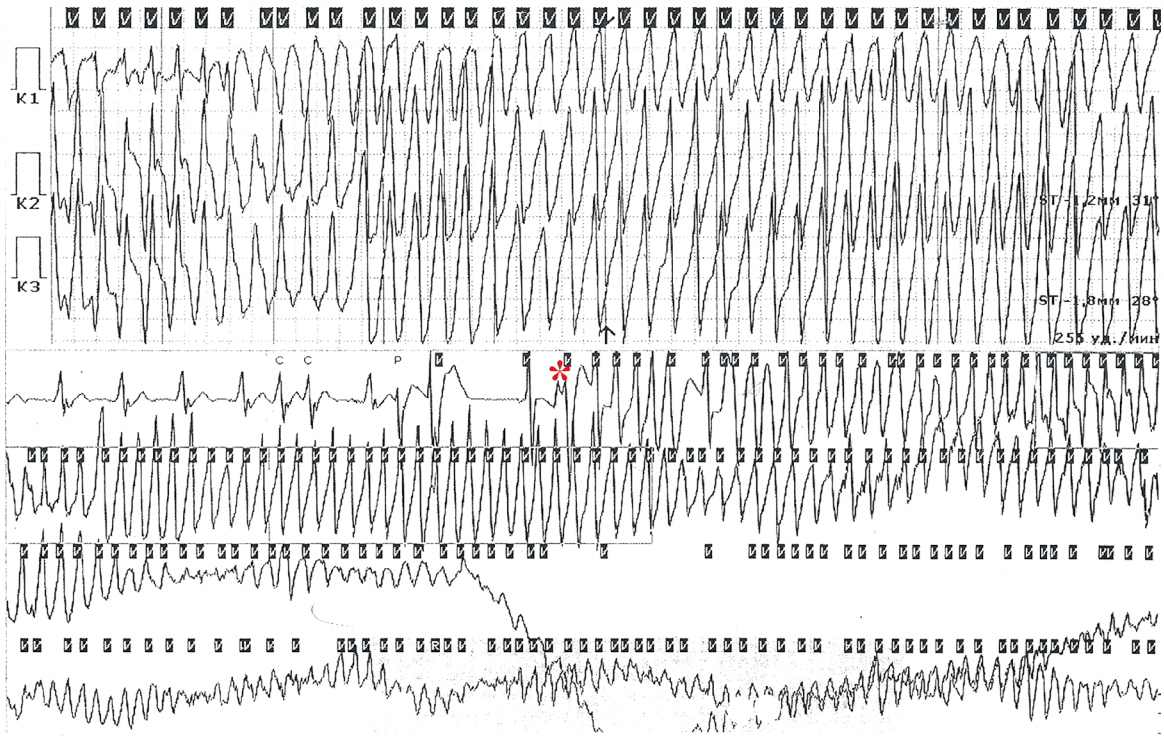

Fig. 5. 24-hour Holter ECG of patient 642c. Ventricular premature beat, *R* on *T* pattern (red asterisk), initiated a paroxysm of ventricular tachycardia with transformation into ventricular fibrillation

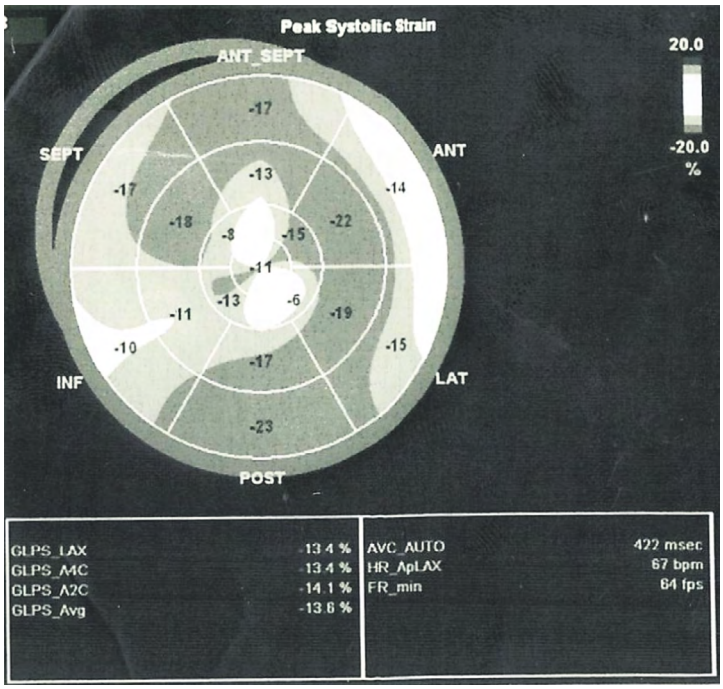

Fig. 6. 2D Speckle Tracking Echocardiography of patient 816. Left ventricular global longitudinal strain — 13,6 %

as indicated by the presence of one of the following variants: 873c, 829, 586, 543, 15m, 732, 799, 642c, 816, 868c, and 590. Pathogenic variants were identified in genes associated with LQTS, SQTS, Brugada syndrome, CPVT, and subclinical manifestations of various cardiomyopathies.

DISCUSSION

In the present study, among 20 patients initially diagnosed with IVF and UCA, the clinical diagnosis of IVF was clarified in 11 (55%) patients by genetic testing. It revealed likely pathogenic variants in the *KCNH2, SCN5A, RYR2*, and *RBM20* genes in 4 (20%) patients. In 7 (35%) patients, variants of unknown clinical significance were found in 10 genes associated with channelopathies and cardiomyopathies. No significant genetic alterations were detected in 9 (45%) out of 20 probands, although 4 had borderline *QTc* values on ECG and 2 had a family history of SCD. Apparently, the absence of genetic disorders in these patients may be due to the localization of diagnostically significant mutations in introns or in other genes not included in the research panel, or extensive deletions, the detection of which by the NGS method is challenging.

Genetic alterations associated with LQTS (30%) were common in patients with UCA, with only one patient exhibiting a mutation in the *KCNH2* gene having *QTc* prolongation up to 500 ms on one ECG series. In other patients with substitutions in the *ANK2* gene and a mutation in the *AKAP9* gene, the *QTc* interval was ⩽ 440 ms. Furthermore, the pathogenic mutation in the *CACNA1C* gene was not associated with *QTc* prolongation and other noncardiac manifestations suggestive of Timothy syndrome. Therefore, without genotyping, early diagnosis before the development of a life-threatening arrhythmic event is challenging.

The clinical phenotype of CPVT in proband 642 before age 15 years was not manifested by polymorphic nonsustained VT characteristic of this pathology, which is triggered by physical activity or emotion. Genetic testing after the development of the event revealed a mutation in the *RYR2* gene, which allowed the diagnosis to be changed to CPVT.

In two patients in whom the disease manifested with the development of VF, genotyping revealed a likely pathogenic variant in the *SCN5A* gene and substitution in the *SCN10A* gene. The spontaneous Brugada pattern was recorded on ECG at the time of the arrhythmic event with no further signs of this disorder on serial ECGs. Owing to genetic study, the diagnosis of IVF was changed to Brugada syndrome.

It is noteworthy that genotyping of patients with IVF revealed genetic variants associated with cardiomyopathies; however, the patients exhibited no obvious clinical phenotype during VF.

The results of genetic testing in patients who had UCA showed a pathogenic or likely pathogenic variant in 20% of cases. These findings demonstrate that a genetic heart disease can manifest as a life-threatening arrhythmia even in the absence of a clear clinical phenotype. Therefore, genetic testing is crucial in patients who have had UCA/IVF. The identification of a clinical phenotype in genotyped probands facilitates detection of more pathogenic variants. This is due to genetic alterations identified in the patient allow for cascade screening of family members, during which segregation analysis may confirm the pathogenicity of some variants with unknown clinical significance. Conversely, in

patients without an identifiable clinical phenotype, the test results may remain negative [17].

However, VUS remain a challenging problem in clinical practice, requiring considerable time, resources, and experience to resolve [18]. In our research, VUS were detected in 7 (35%) patients. Studies on molecular autopsy using large gene panels in investigating sudden arrhythmic death syndrome, which can be considered equivalent to UCA/IVF, showed comparable results. Nunn et al. reported that in a set of 135 genes in 59 patients with sudden arrhythmic death syndrome, 29% of patients had likely pathogenic variants and 34% had VUS [19]. Bagnall et al. reported a 27% efficiency when testing 59 genes in 113 cases of unexplained SCD [20].

Our results indicate that genetic testing is recommended for all patients with UCA, with or without evidence of cardiovascular disease. Long-term prospective studies with a large cohort of genotyped UCA patients and their families are required to determine the potential role of genetic variants in risk stratification. A better understanding of genotype–phenotype association is favorable in determining the contribution of VUS and identifying more reliable criteria for assessing pathogenicity.

CONCLUSIONS

The data from our study are intended to convey that cardiac channelopathies and subclinical manifestations of cardiomyopathies are common causes of disease in IVF patients with UCA, which require genetic testing in this group of patients. Genotyping of UCA patients revealed genetic changes associated with LQTS in 30% of cases. The *QTc* interval did not exceed 440 ms in most cases, making early diagnosis before the development of a life-threatening arrhythmic event challenging. Identifying the underlying genetic variant responsible for cardiac arrest may be beneficial in clarifying the clinical diagnosis, providing individualized treatment, and facilitating cascade screening of other at-risk family members.

STUDY LIMITATIONS

This study had several limitations. Firstly, the study sample was relatively small. Secondly, the final cohort included only patients who survived UCA referred for genetic testing. Finally, the lack of the clinical and genetic data of family members prevents a more precise interpretation of the impact of the identified variants, including those of unknown clinical significance.

ADDITIONAL INFORMATION

Ethics approval. The protocol of the study was approved by Institute of Genetics and Cytology of Belarus National Academy of Sciences Ethics Committee, protocol No. 2, 08.06.2021. Written consent was obtained from the patient for publication of relevant medical information and all accompanying images within the manuscript.

Author contribution. Thereby, all authors confirm that their authorship complies with the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research, and preparation of the article, as well as read and approved the final version before its publication). Personal contribution of the authors: S.M. Komissarova — concept and design of the study, writing — original draft, patient follow-up; N.N. Chakova — conducting and interpreting the results of genetic analysis, writing — original draft; N.M. Rineiska — data curation, diagnostic studies, writing — original draft, review and editing, literature review; S.S. Niyazova — conducting and interpreting the results of the genetic analysis; T.V. Dolmatovich — conducting and interpreting the results of the genetic analysis; V.Ch. Barsukevich — patient follow-up; L.I. Plaschinskaya — diagnostic studies.

Competing interests. The authors declare that they have no competing interests.

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Заключение этического комитета. Протокол исследования был одобрен этическим комитетом Института генетики и цитологии Национальной академии наук Беларуси (протокол № 2 заседания Комитета по биоэтике от 08.06.2021). Авторы получили письменное согласие законных представителей пациентов на публикацию медицинских данных и фотографий.

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Вклад каждого автора: С.М. Комиссарова — концепция и дизайн исследования, написание текста, динамическое наблюдение за пациентами; Н.Н. Чакова — проведение и интерпретация результатов генетического анализа пациентов, написание текста; Н.М. Ринейская — анализ полученных данных, диагностические исследования, написание текста, обзор литературы; С.С. Ниязова — проведение и интерпретация результатов генетического анализа пациентов; Т.В. Долматович — проведение и интерпретация результатов генетического анализа пациентов; В.Ч. Барсукевич — динамическое наблюдение за пациентами; Л.И. Плащинская — диагностические исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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Genetic markers and traditional risk factors in predicting atrial fibrillation in patients with arterial hypertension, focus on the renin-angiotensin-aldosterone system genes

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ABSTRACT

BACKGROUND: Genetic and environmental factors are involved in the development of atrial fibrillation in arterial hypertension. This determines the relevance of studying gene-environment interactions in the occurrence of arrhythmia.

AIM: To evaluate the contribution of the renin-angiotensin-aldosterone system genes polymorphisms to the susceptibility to atrial fibrillation in patients with arterial hypertension, and also to study the combined influence of these polymorphisms and environmental factors on the risk of arrhythmia.

MATERIALS AND METHODS: The study included 60 patients with arterial hypertension and paroxysmal atrial fibrillation (study group), 60 patients with arterial hypertension without atrial fibrillation (comparison group 1) and 20 healthy volunteers (comparison group 2). Angiotensin-converting enzyme (*ACE* (*I/D*)) and angiotensin II type 1 receptor gene (*AGTR1* (*A1166C*)) polymorphisms were analyzed by real-time polymerase chain reaction.

RESULTS: Genotype II and allele I of the *ACE* gene *(I/D)* in patients with arterial hypertension and atrial fibrillation were significantly more frequent compared to patients with arterial hypertension without arrhythmia ($\chi^2 = 4.547$; $p = 0.03$ and $\chi^2 = 4.818$; $p = 0.03$ respectively). Carriage of genotype II in patients with arterial hypertension increased the chance of developing atrial fibrillation by 2.8 times (95% CI 1.19–7.18). The odds ratio (OR) for arrythmia development in patients with arterial hypertension and allele I was 1.8 (95% CI 1.10–3.07). The presence of obesity in patients with arterial hypertension in the presence of genotype II of the *ACE* gene *(I/D)* was associated with an increased risk of developing atrial fibrillation, compared with the genotype alone (OR = 4.16, 95% CI 1.16–19.87). A study of the A1166C polymorphism of the *AGTR1* gene did not reveal a reliable significant relationship between its inheritance and the development of atrial fibrillation.

CONCLUSION: Genotype II and allele I of the *ACE* gene *(I/D)* were statistically significantly more frequent in patients with arterial hypertension and atrial fibrillation. Carriage of genotype II and allele I of the *ACE* gene *(I/D)* increased the chance of developing atrial fibrillation in patients with arterial hypertension. Obesity had a significant effect on the susceptibility to atrial fibrillation in the presence of genotype II of the *ACE* gene *(I/D)* in hypertensive patients.

Keywords: atrial fibrillation; arterial hypertension; renin-angiotensin-aldosterone system; gene polymorphism; risk factor; obesity.

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Генетические маркеры и традиционные факторы риска в прогнозировании фибрилляции предсердий у пациентов с артериальной гипертензией, фокус на гены ренин-ангиотензин-альдостероновой системы

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АННОТАЦИЯ

Актуальность. В развитие фибрилляции предсердий при артериальной гипертензии вовлечены генетические и средовые факторы. Это определяет актуальность изучения генно-средовых взаимодействий при возникновении аритмии.

Цель исследования — оценить вклад полиморфизмов генов ренин-ангиотензин-альдостероновой системы в предрасположенность к фибрилляции предсердий у пациентов с артериальной гипертензией, а также изучить сочетанное влияние данных полиморфизмов и средовых факторов на риск развития аритмии.

Материалы и методы. В исследовании участвовали 140 человек: 60 пациентов с артериальной гипертензией и пароксизмальной формой фибрилляции предсердий (исследуемая группа), 60 пациентов с артериальной гипертензией без фибрилляции предсердий (группа сравнения 1) и 20 здоровых добровольцев (группа сравнения 2). Анализ полиморфизма гена ангиотензинпревращающего фермента (*ACE (I/D)*) и гена рецептора ангиотензина II 1 типа (*AGTR1 (A1166C)*) выполнен методом полимеразной цепной реакции в режиме реального времени.

Результаты. Генотип II и аллель I гена *ACE (I/D)* у пациентов с артериальной гипертензией и фибрилляции предсердий встречались значимо чаще по сравнению с пациентами с артериальной гипертензией без аритмии ($\chi^2 = 4{,}547$; $p = 0{,}03$ и $\chi^2 = 4{,}818$; $p = 0{,}03$ соответственно). Носительство генотипа II у пациентов с артериальной гипертензией увеличивало шанс развития ФП в 2,8 раза (отношение шансов = 2,83; 95 % доверительный интервал 1,19–7,18). Отношение шансов развития аритмии у пациентов с артериальной гипертензией и аллелем I составило 1,83 (95 % доверительный интервал 1,10–3,07). Наличие ожирения у пациентов с артериальной гипертензией в присутствии генотипа II гена *ACE (I/D)* сопровождалось повышением риска развития фибрилляции предсердий, по сравнению с учетом только генотипа (отношение шансов = 4,16; 95 % доверительный интервал 1,16–19,87). Исследование полиморфизма *A1166C* гена *AGTR1* не выявило достоверно значимой связи между его наследованием и развитием фибрилляции предсердий.

Заключение. Генотип II и аллель I гена *ACE (I/D)* статистически значимо чаще встречались у пациентов с артериальной гипертензией и фибрилляцией предсердий. Носительство генотипа II и аллели I гена *ACE (I/D)* увеличивало шанс развития фибрилляции предсердий у пациентов с артериальной гипертензией. Ожирение оказывало значимое влияние на предрасположенность к фибрилляции предсердий при наличии генотипа II гена *ACE (I/D)* у больных гипертонией.

Ключевые слова: фибрилляция предсердий; артериальная гипертензия; ренин-ангиотензин-альдостероновая система; полиморфизм гена; фактор риска, ожирение.

Как цитировать

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INTRODUCTION

Atrial fibrillation (AF) is a common arrhythmia, occurring in 3%–4% of the general population [1]. It frequently manifests along with arterial hypertension (AH). In a Russian study (n = 2577), the prevalence of AH in patients with established AF aged <60 years was 63.8%, whereas in individuals aged >60, it was 90.1% [2]. Similar results were obtained in the Kazakh population, where the prevalence of AH among patients with arrhythmia reached 86.2% [3].

The development of AF in patients with AH is due to the interaction of genetic and environmental factors. Among these, the most common are obesity, smoking, hypercholesterolemia, and hyperuricemia. A meta-analysis of 16 studies involving 123,249 patients demonstrated a correlation between elevated body mass index (BMI) and AF risk. Overweight and obese individuals have a 39% and 87% greater risk of arrhythmia, respectively, compared to those with normal BMI [4]. General and abdominal obesity were found to increase the risk of AF. In patients with AH, increased waist circumference (WC) was identified as a predictor of AF (Odds Ratio (OR) = 1.07; 95% CI: 1.04–1.10) [5]. The Rotterdam Study showed that former and current smokers were equally at risk of developing arrhythmias [6]. The 16-year prospective Atherosclerosis Risk in Communities Study found that former and continuing smokers had a 32% and 105% higher risk, respectively, of developing AF compared with those who had never smoked [5]. The contribution of hypercholesterolemia to the development of AF is uncertain. However, a correlation between reduced levels of high-density lipoprotein cholesterol (HDL-C) and AF has been noted. For example, a Japanese study involving 28,449 people without arrhythmia at inclusion found that low HDL-C levels were associated with the development of AF in women [7]. A meta-analysis of six cohort studies demonstrated a significant association between hyperuricemia and increased AF risk (OR = 1.49; 95% CI: 1.24–1.79; $p < 0.001$) [8].

Among neurohumoral factors, activation of the renin–angiotensin–aldosterone system (RAAS) is associated with the development of AF. RAAS activity is genetically determined. One of the key links of RAAS is angiotensin-converting enzyme (ACE), which forms the main vasoconstrictor — angiotensin II (AT-II). The effects of the latter are mainly induced by the influence on type 1 receptors. The polymorphism of the ACE type I/D gene (*ACE* (*I/D*)) in the 16th intron of chromosome 17 is associated with the activity of the enzyme in the blood. An increase in the latter results in increased AT-II production, which contributes to the development of AF [9]. The gene encoding the type 1 AT-II receptor (*AGTR1* (*A1166C*)) is located on chromosome 3 (3q24). The substitution of adenine (A) for cytosine (C) at position 1166 of the *AGTR1* gene affects the functional activity of the AT-II receptor. Homozygotes for the allelic variant C of this gene shows a higher affinity for AT-II [9]. Data on the effect of polymorphisms of the *ACE* type *I/D* gene and the gene encoding the type 1 AT-II receptor (*AGTR1* (*A1166C*)) on ACE activity and the functional activity of the receptor are inconclusive and contradictory.

This study aimed to assess the role of RAAS gene polymorphisms in predisposition to AF in patients with AH and investigate the combined effect of these polymorphisms and environmental factors on the risk of arrhythmia development.

MATERIALS AND METHODS

Overall, 120 patients with AH grades I and II were examined. Of these, 60 patients had a paroxysmal form of AF and comprised the study group (SG), and 60 had no AF and comprised comparison group 1 (CG-1). Comparison group 2 (CG-2) included 20 healthy volunteers. The exclusion criteria were AH grade III, symptomatic AH, clinically significant forms of ischemic heart disease, non-coronary myocardial diseases, heart defects, heart rhythm disorders (ventricular extrasystole above Lown class 2, Wolff – Parkinson – White syndrome), radiofrequency ablation before the study, acute inflammatory diseases, chronic heart failure with functional class II or higher, thyroid dysfunction, chronic kidney disease with a glomerular filtration rate ⩽60 ml/min/1.73 m^2, liver dysfunction, diabetes mellitus, cancer, and other severe comorbidities that can affect the parameters under study.

The identification of risk factors (RFs) included the assessment of the incidence of smoking, obesity, hypercholesterolemia, and hyperuricemia. Smoking status was determined using a questionnaire. Individuals were considered smokers if they were past or current smokers. All patients were measured for WC, hip circumference (HC), WC/HC ratio, height, and weight, with subsequent BMI calculation. WC was assessed in the standing position by placing a centimeter tape on the midpoint of the distance between the crest of the iliac bones and lower edge of the ribs. HC was measured at the most protruding points of the buttocks. The presence of abdominal obesity was established when the WC was >88 cm in women and >102 cm in men. A BMI ⩾ 30 kg/m^2 indicated obesity [10].

Blood plasma lipid parameters and serum uric acid levels were assessed using Diazens reagents (Belarus) on an automated photometer RA 2600 (CJSC SOLAR, Belarus). Hypercholesterolemia was determined when the total cholesterol level was ⩾ 4.9 mmol/L and/or hypolipidemic therapy was used [10]. Hyperuricemia was defined as an increase in uric acid level of >360 μmol/L [10].

Polymerase chain reaction (PCR) method was used to identify polymorphic markers of RAAS genes: *ACE (I/D)* and *AGTR1* (*A1166C*). Genomic DNA was extracted from collected blood samples using vacuum systems with ethylenediaminetetraacetate and a set of reagents for DNA extraction from whole blood by M-sorb magnetic sorption method (Syntol LLC, Russia). Genotyping was conducted via real-time PCR on a Rotor-Gene Q 5plex HRM thermocycler

system (QIAGEN, Germany). In the analysis of obtained results, the conformity of the control genotypes with the declared ones was verified.

Statistical analysis was conducted using the Statistica 10.0 application program package. The results are presented as the median (Me) and interquartile range [*LQ*; *UQ*]. The Mann – Whitney *U* test was used to compare two independent groups. Multiple comparisons within groups (more than two) were performed using the Kruskal–Wallis *H*-criterion. The category distributions between groups was compared using Pearson's χ^2 homogeneity criterion. In the case of two compared groups and two categories, the Yates correction for Pearson's χ^2 criterion was used. If the conditions for employing Pearson's chi-squared homogeneity criterion were not met, Fisher's exact test was employed. The ORs of pathology development under and without the influence of RFs were defined as exponents of the corresponding regression coefficients in the logistic regression equations. In these equations, the independent variable was a binary indicator variable (risk factor present/no risk factor present), and the dependent variable was a binary indicator (pathology development present/no pathology development). The 95% CI for ORs was calculated as the exponent of the corresponding CI for the regression coefficients. The threshold value for the statistical significance was assumed to be 0.05. To test the independence of the RFs when accounting for their joint influence on the dependent variable, the generalized variance inflation factor (generalized VIF) was determined. If the condition generalized VIF2 was < 4 was, the RFs were considered independent.

RESULTS AND DISCUSSION

The studied groups did not differ in age and were comparable in gender. Table 1 shows the comparative characteristics of the groups.

The duration of history of AH was significantly higher in SG patients than in CG-1 patients ($p = 0.002$). Regarding BMI, WC, HC, and WC/HC, SG was comparable to CG-1. Healthy volunteers had significantly lower BMI, WC, and HC compared to patients with AH and paroxysmal AF and AH patients without arrhythmia ($p = 0.0000$ for all values). As regards WC/HC, CG-2 was comparable to CG-1 and significantly different from SG ($p = 0.02$).

Table 2 presents the frequency of the primary RFs for cardiovascular disease (CVD). No significant differences were found in the groups by smoking status. However, a tendency for a higher frequency of smoking were noted among patients with AF with/without AH compared to healthy individuals.

Obesity was significantly more common in SG and CG-1 than in CG-2 ($p < 0.05$). Abdominal obesity was equally frequent in SG and CG-1 and was diagnosed less frequently in CG-2 ($p < 0.05$).

Hypercholesterolemia was the most common factor in all studied groups. It was significantly less frequent in CG-2 than in CG-1 ($p < 0.05$). Hyperuricemia was two times more common in SG and CG-1 than in CG-2; however, the differences were not significant.

The distribution of genotype and allele frequencies for polymorphisms of the studied genes in the SG and

Table 1. General characteristics of the examined groups

Patient groups	Study group (*n* = 60)	Comparison group 1 (*n* = 60)	Comparison group 2 (*n* = 20)
Age, years	61 [58; 62.5]	60 [57; 62]	59 [56; 61]
Women, *n* (%)	31 (51.7)	31 (51.7)	10 (50)
Duration of arterial hypertension, years	16 [12; 22.5] [2]	11 [7; 18.5] [1]	–
Arterial hypertension grade I, *n* (%)	24 (40)	23 (38.3)	–
Arterial hypertension grade II, *n* (%)	36 (60)	37 (61.7)	–
Duration of atrial fibrillation, years	5 [3; 8]	–	–
Body mass index, kg/m^2	30.8 [28.1; 34.0][3]	29.7 [27.6; 32.8][3]	24.5 [22.1; 26.3][1.2]
Waist circumference, cm	106.5 [99.0; 111.5][3]	102.0 [96.0; 106.5][3]	92.0 [80.0; 94.5][1.2]
Hip circumference, cm	113.0 [108.5; 121.0][3]	112.0 [107.0; 118.5][3]	102.5 [99.0; 105.0][1.2]
Waist circumference/ hip circumference	0.92 [0.88; 0.96][3]	0.9 [0.85; 0.95]	0.89 [0.83; 0.92][1]

Note: [1] — $p < 0.05$, compared to the study group; [2] — $p < 0.05$, when compared to comparison group 1; [3] — $p < 0.05$, when compared to comparison group 2.

CGs corresponded to the Hardy – Weinberg equilibrium ($p > 0.05$). Table 3 shows the results obtained by analyzing the genotypes and alleles of the *ACE* gene (*I/D*). Genotype II was more common in patients with AH and AF than in patients with AH without arrhythmia (33.3% and 15.0%, respectively; $\chi^2 = 4.547$; $p = 0.03$). No significant difference was noted in the frequency of genotype II between SG and CG-2 (33.3% and 30%, respectively; $\chi^2 = 0.000$; $p = 1.0$). However, allele I was significantly more frequent in SG than in CG-1 ($\chi^2 = 4.818$; $p = 0.03$). The high frequency of genotype II and allele I in healthy volunteers compared to that in CG-1 was notable (30% vs. 15% and 55% vs. 41.7%, respectively); however, these differences were not significant.

The OR of AF development in patients with AH and genotype II of the *ACE* gene (*I/D*) was 2.83 (95% CI, 1.19–7.18), respectively. Consequently, patients with AH and genotype II of the *ACE* gene (*I/D*) were 2.8 times more likely to develop AF compared to patients with AH and genotype ID or DD. Furthermore, carriage of allele I in patients with AH increased the risk of AF by 1.8-fold (OR = 1.83; 95% CI, 1.10–3.07).

Table 4 displays the frequency of genotypes and alleles of the *AGTR1* (*A1166C*) gene. Differences in the frequency of occurrence of genotypes and alleles of *AGTR1* (*A1166C*) gene between groups were not significant.

In the subsequent phase of the study, the correlation between the *ACE* gene I/D polymorphism and *AGTR1* gene

Table 2. Frequency of cardiovascular diseases risk factors in the examined groups

Parameters	Study group (*n* = 60)		Comparison group 1 (*n* = 60)		Comparison group 2 (*n* = 20)	
	n	%	*n*	%	*n*	%
Smoking status	23	38.3	20	33.3	4	20
Abdominal obesity	47	78.3[3]	47	78.3[3]	4	20[1, 2]
Obesity	37	61.7[3]	29	48.3[3]	0	0[1, 2]
Increased total cholesterol	52	86.7[3]	51	85[3]	12	60[1, 2]
Hyperuricemia	20	33.3	21	35	3	15

Note: [1] — $p < 0.05$, compared to the study group; [2] — $p < 0.05$, when compared to comparison group 1; [3] — $p < 0.05$, when compared to comparison group 2.

Table 3. Distribution of genotypes and alleles of the *ACE (I/D)* gene in patients of the studied groups

Genetic variant	Study group (*n* = 60)		Comparison group 1 (*n* = 60)		Comparison group 2 (*n* = 20)	
	n	%	*n*	%	*n*	%
DD genotype	12	20	19	31.7	4	20
ID genotype	28	46.7	32	53.3	10	50
II genotype	20*	33.3	9*	15.0	6	30
D allele	52	43.3	70	58.3	18	45
I allele	68*	56.7	50*	41.7	22	55

Note: * — statistically significant differences ($p < 0.05$) of genotype and allele frequencies in the study group compared to those in comparison group 1.

Table 4. Distribution of genotypes and alleles of the *AGTR1 (A1166C)* gene in patients of the studied groups

Genetic variant	Study group (*n* = 60)		Comparison group 1 (*n* = 60)		Comparison group 2 (*n* = 20)	
	n	%	*n*	%	*n*	%
CC genotype	9	15	4	6.7	4	20.0
AC genotype	26	43.3	23	38.3	9	45.0
AA genotype	25	41.7	33	55.0	7	35.0
C allele	44	36.7	31	25.8	17	42.5
A allele	76	63.3	89	74.2	23	57.5

A1166C polymorphism and AF onset was examined, with consideration of the influence of traditional RFs. Table 5 illustrates the distribution of *ACE* gene genotypes (*I/D*) across the studied groups, in the presence or absence of specific factors including smoking, hypercholesterolemia, hyperuricemia, and general and abdominal obesity.

In the context of obesity, genotype II was 3.2 times more prevalent ($p < 0.05$) in SG than in CG-1. Furthermore, in the presence of hypercholesterolemia, genotype II was 2.2 times more frequent ($p < 0.05$) in SG than in CG-1. Notably, no differences were observed in the frequency of *ACE* gene genotypes among smoking patients in SG and CG-1. However, genotype II was significantly more common among never-smoking patients with AH and paroxysmal AF than in those with AH without arrhythmia ($p < 0.05$).

The results of the OR calculation indicated an association between cardiovascular risk factors and the risk of AF development in *ACE* genotype II carriers (*I/D*). The risk of AF development at genotype II carriage in patients with AH and hypercholesterolemia was 2.8 (OR = 2.79; 95% CI, 1.13–7.38). Consequently, including cholesterol levels in the evaluation of carriers of this genotype did not result in an increased risk of arrhythmia compared to that in the evaluation of genotype II alone (OR = 2.83; 95% CI, 1.19–7.18). Obesity was associated with a greater increase in the risk of AF in genotype II carriers with AF than in genotype II carriers alone (OR = 2.83; 95% CI, 1.19–7.18).

The simultaneous accounting of the influence of two RFs on the probability of AF development can be achieved by developing a two-factor logistic regression model. In this model, the binary variable "no AF/have AF" is considered to depend on two predictors: the binary variables "genotype not II/genotype II" and "no obesity/have obesity". Table 6 presents the statistics of regression coefficients and AUC of this model.

Because only 24% of the subjects were carriers of genotype II, the weight function *W* was used to determine the coefficients of the regression equation, with a value of 3 assigned to subjects who were carriers of genotype II and 1 to subjects who were not (the sample was balanced with respect to the variables "no AF/have AF" and "no obesity/have obesity").

To test the hypothesis on the independence of variables in the above equation, the generalized VIF for this regression

Table 5. Occurrence of risk factors in the studied groups depending on the genotype of the *ACE* (*I/D*) gene

Risk factor or lack thereof	Study group ($n = 60$)			Comparison group 1 ($n = 60$)			Comparison group 2 ($n = 20$)		
	DD	*ID*	*II*	*DD*	*ID*	*II*	*DD*	*ID*	*II*
Smoking, *n* (%)	5 (21.7)	12 (52.2)	6 (26.1)	6 (30.0)	11 (55.0)	3 (15.0)	1 (25.0)	3 (75.0)	– (0.0)
Nonsmokers, *n* (%)	7 (18.9)	16 (43.2)	14* (37.8)	13 (32.5)	21 (52.5)	6* (15.0)	3 (18.75)	7 (43.75)	6 (37.5)
Abdominal obesity, *n* (%)	7 (14.9)	24 (51.1)	16 (34.0)	16 (34.0)	24 (51.1)	7 (14.9)	1 (25.0)	3 (75.0)	–
Normal waist circumference, *n* (%)	5 (38.5)	4 (38.75)	4 (38.75)	3 (23.1)	8 (61.5)	2 (15.4)	3 (18.75)	7 (50.0)	6 (46.15)
Obesity, *n* (%)	7 (18.9)	18 (48.6)	12* (32.4)	9 (31.0)	17 (58.6)	3* (10.3)	– (0.0)	– (0.0)	– (0.0)
No obesity, *n* (%)	5 (21.7)	10 (43.5)	8 (34.8)	10 (32.3)	15 (48.4)	6 (19.3)	4 (20.0)	10 (50.0)	6 (30.0)
Hyperuricemia, *n* (%)	6 (30.0)	7 (35.0)	7 (35.0)	6 (28.6)	12 (57.1)	3 (14.3)	2 (66.7)	1 (33.3)	– (0.0)
Normal uric acid levels, *n* (%)	6 (15.0)	21 (52.5)	13 (32.5)	13 (33.3)	20 (51.3)	6 (15.4)	2 (11.8)	9 (52.9)	6 (35.3)
Hypercholesterolemia, *n* (%)	10 (19.2)	24 (46.2)	18* (34.6)	17 (33.3)	26 (51.0)	8* (15.7)	1 (8.3)	6 (50.0)	5 (41.7)
Normal total cholesterol levels, *n* (%)	2 (25.0)	4 (50.0)	2 (25.0)	2 (22.2)	6 (66.7)	1 (11.1)	3 (37.5)	4 (50.0)	1 (12.5)

Note: *— significant differences ($p < 0.05$) in the frequency of occurrence of genotypes and alleles in the study group compared to comparison group 1.

Table 6. Statistics of the regression coefficients and AUC of the model

Indicators	Score	Standard deviation	*p*	OR	95% CI for OR	AUC (95 % CI)
Constant term	–0.6748	0.2857	0.0018	–	–	0.631 (0.538–0.724)
Genotype II "yes"	1.1105	0.3218	0.0006	3.04	1.63–5.78	
Obesity "yes"	0.7535	0.3208	0.0188	2.12	1.14–4.02	

Note: CI — confidence interval; OR — odds ratio.

Table 7. Occurrence of risk factors in the studied groups depending on the genotype of the *AGTR1 (A1166C)* gene

Risk factor or lack thereof	Study group (*n* = 60)			Comparison group 1 (*n* = 60)			Comparison group 2 (*n* = 20)		
	CC	*AC*	*AA*	*CC*	*AC*	*AA*	*CC*	*AC*	*AA*
Smoking, *n* (%)	4 (17.4)	11 (47.8)	8 (34.9)	2 (10.0)	8 (40.0)	10 (50.0)	1 (25.0)	3 (75.0)	– (0.0)
Nonsmokers, *n* (%)	5 (13.5)	15 (40.5)	17 (46.0)	2 (5.0)	15 (37.5)	23 (57.5)	3 (18.75)	6 (37.5)	7 (43.75)
Abdominal obesity, *n* (%)	8 (17.0)	19 (40.4)	20 (42.6)	3 (6.4)	18 (38.3)	26 (55.3)	– (0.0)	3 (75.0)	1 (25.0)
Normal waist circumference, *n* (%)	1 (7.7)	7 (53.8)	5 (38.5)	1 (7.7)	5 (38.5)	7 (53.8)	4 (25.0)	6 (37.5)	6 (37.5)
Obesity, *n* (%)	7 (18.9)	13 (35.1)	17 (45.9)	2 (6.9)	11 (37.9)	16 (43.2)	– (0.0)	– (0.0)	– (0.0)
No obesity, *n* (%)	2 (8.7)	13 (56.5)	8 (34.8)	2 (6.5)	12 (38.7)	17 (54.8)	4 (20.0)	9 (45.0)	7 (35.0)
Hyperuricemia, *n* (%)	2 (10.0)	10 (50.0)	8 (40.0)	1 (4.8)	8 (38.1)	12 (57.1)	1 (33.3)	2 (66.7)	– (0.0)
Normal uric acid levels, *n* (%)	7 (17.5)	16 (40.0)	17 (42.5)	3 (7.7)	15 (38.5)	21 (53.8)	3 (17.6)	7 (41.2)	7 (41.2)
Hypercholesterolemia, *n* (%)	9 (17.3)	21 (40.4)	22 (42.3)	4 (7.8)	20 (39.2)	27 (52.9)	3 (25.0)	3 (25.0)	6 (50.0)
Normal total cholesterol levels, *n* (%)	– (0.0)	5 (62.5)	3 (37.5)	– (0.0)	3 (33.3)	6 (66.7)	1 (12.5)	6 (75.0)	1 (12.5)

model was calculated, which was 1.02. generalized VIF^2 was < 4, indicating that the predictors in the equation that consider their joint influence on the outcome (presence of AF) are mathematically independent.

Table 7 illustrates the prevalence of *AGTR1* (*A1166*) genotypes in relation to the presence of environmental factors. However, no significant differences were observed between the subgroups when environmental factors were included.

DISCUSSION

The associations between genotype II and allele I of the *ACE* gene (*I/D*) and risk of developing AF differed from those observed in other populations. In the Tunisian population, the DD genotype was associated with a 3.41-fold increased risk of AF (OR = 3.41; 95% CI, 1.39–8.34; $p < 0.007$) [11]. A meta-analysis of 23 studies involving 9,262 patients demonstrated the association between the DD genotype of the *ACE* gene (*I/D*) and AF risk [12]. In contrast, a recent study in a Russian population revealed that carriage of genotype II and allele I increases the risk of developing AF (OR = 3.165; 95% CI, 1.403–7.137 and OR = 2.552; 95% CI, 1.558–4.181, respectively) [13]. This indicates interpopulation differences and underscores the need for further research in the Belarusian population.

However, data on the effect of the *A1166C* polymorphism of the *AGTR1* gene are limited and contradictory. A Russian study found no significant differences in the development of AF from the polymorphism of this gene [14]. Moreover, Chinese scientists obtained data indicating that carriage of the C allele increases the risk of AF development by 1.43 times [15].

Our findings indicate a potential synergistic effect of genotype II and obesity in the pathogenesis of PD through RAAS activation. Currently, adipose tissue is recognized as an active endocrine organ, secreting a multitude of substances, including RAAS components [16].

Moreover, none of the CG-2 patients were obese, and genotype II of the *ACE* gene was not found in factors such as smoking and hyperuricemia. This may further indicate the role of gene-mediated interactions in the development of CVD. Thus, despite the equal frequency of *ACE* gene genotype II in patients with AH and paroxysmal AF and healthy volunteers, the latter do not develop arrhythmias owing to the lack of potentiating effect of environmental factors.

CONCLUSIONS

The presence of genotype II and allele I of the *ACE* gene (*I/D*) in patients with AH increased the risk of AF development by 2.8 and 1.8 times, respectively. Furthermore, obesity in carriers of this genotype was found to increase the risk of AF development by 4.2 times. These findings show that genetic (carriage of genotype II of the *ACE* gene) and environmental factors, primarily obesity, play a significant role in the development of AF in patients with AH. Additionally, the results obtained for *ACE* gene polymorphism (*I/D*) differ from those in other studies, which is probably due to interpopulation differences and requires testing on larger

samples. A better understanding of the relationship between genetic polymorphisms and traditional cardiovascular RFs provides more opportunities for personalized diagnosis and identification of patients at high risk for AF.

ADDITIONAL INFORMATION

Author contribution. All authors made significant contributions to the conception, research and preparation of the article, and read and approved the final version before publication. Personal contribution of the authors: N.V. Bukvalnaya — collection of the material, statistical processing, results interpretation of the results obtained, text writing; L.V. Yakubova — concept and design of the article, text editing; A.V. Kapytski — statistical processing, text editing; L.V. Kezhun — collection of the material, results interpretation; O.V. Gorchakova — definition of polymorphisms, text editing; D.G. Karnialiuk — collection of the material, results interpretation; E.Yu. Charnetskaya — determination of total cholesterol and uric acid levels in blood serum; V.A. Snezhitskiy — literature review, final approval of the manuscript for publication.

Competing interests. The authors declare that they have no competing interests.

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Informed consent for publication. Written consent was obtained from the patients and healthy volunteers for publication of medical data.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Вклад каждого автора: Н.В. Буквальная — сбор материала, статистическая обработка, интерпретация полученных результатов, написание текста; Л.В. Якубова — концепция и дизайн статьи, редактирование текста; А.В. Копыцкий — статистическая обработка, редактирование текста; Л.В. Кежун — сбор материала, интерпретация полученных результатов; О.В. Горчакова — определение полиморфизмов, редактирование текста; Д.Г. Корнелюк — сбор материала, интерпретация полученных результатов; Е.Ю. Чернецкая — определение уровня общего холестерина и мочевой кислоты в сыворотке крови; В.А. Снежицкий — обзор литературы, окончательное утверждение рукописи для публикации.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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An arrhythmic variant of the manifestation of paraneoplastic Loeffler endomyocarditis. Clinical case

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ABSTRACT

A clinical case of chronic undulating course of parneoplastic Loeffler endomyocarditis, the leading manifestations of which were ventricular arrhythmias, is presented. The paper demonstrates the complexity of early diagnosis of a rare pathology in a polymorbid patient and attempts to identify the "keys" to the correct diagnostic and therapeutic tactics for managing such patients.

Keywords: hypereosinophilic syndrome; hypereosinophilia; reciprocal ventricular tachycardia; Loeffler endocarditis; eosinophilic myocarditis.

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Аритмический вариант манифестации паранеопластического эндомиокардита Леффлера. Клинический случай

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АННОТАЦИЯ

Представлен клинический случай хронического волнообразного течения парнеопластического эндомиокардита Леффлера, ведущими проявлениями которого стали желудочковые нарушения ритма. В работе демонстрируется сложность ранней диагностики редкой патологии у полиморбидного пациента и предпринимается попытка определить «ключи» к верной диагностической и лечебной тактике ведения подобных пациентов.

Ключевые слова: гиперэозинофильный синдром; гиперэозинофилия; реципрокная желудочковая тахикардия; эндокардит Леффлера; эозинофильный миокардит.

Как цитировать

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INTRODUCTION

Loeffler endomyocarditis (LEM) is a cardiac manifestation of hypereosinophilic syndrome (HES), wherein hypereosinophilia (eosinophil count >1500/μL) [1] and target-organ damage are obligatory components, caused by the degranulation of large numbers of eosinophils with the release of significant amounts of cytokines (i.e., interleukin (IL)-3, IL-5, and granulocyte-macrophage colony-stimulating factor) into organs and tissues [2–5].

The presence of characteristic echocardiographic signs allows the accurate diagnosis of LEM at late stages[6,7]; however, the course of the disease at these stages is typically irreversible. Early diagnosis is challenging owing to the absence of overt and unambiguous symptoms. Nevertheless, early diagnosis and prompt intervention can prevent irreversible structural changes. We present a case of confirmed LEM wherein the initial clinical manifestation was recurrent ventricular rhythm disturbances.

CLINICAL CASE

A 60-year-old man was first admitted to St. Petersburg City Pokrovskaya Hospital in January 2023 with a ventricular tachycardia (VT) paroxysm. The ambulance team attempted to medically control the VT; however, this was ineffective, as were three subsequent defibrillator discharges, after which the patient was admitted to hospital. In the hospital, VT persisted after intravenous administration of 300 mg of amiodarone and was treated by electrical cardioversion (ECV). The electrocardiography (ECG) record of the first VT was lost; however, its description was preserved in the documents: the frequency of the VT was 176 beats per minute (bpm), QRS complex had the form of complete block of the right bundle branch (RBBB) and left anterior fascicular branch (LAFB) (left VT), and QRS width was 150 ms.

The patient's medical history showed that the patient had suffered a non-ST elevation myocardial infarction in 2008 and underwent an anterior interventricular artery (AIVA) stenting the same year and a coronary artery bypass graft (CABG) in 2012. No ventricular rhythm disturbances were recorded until January 2023. At the first hospitalization in January 2023, VT occurrence was attributed to coronary heart disease (CHD) and post-infarction cardiosclerosis. The patient refused further evaluation and treatment and was discharged at his own request on hospitalization day 2.

Additionally, the patient had a history of peripheral carcinoma of the right lung, for which a right lung lobectomy was performed in 2014. In 2021, the patient underwent radiation therapy for carcinoma of the left lung. In December 2022, metastases to the pleura, lymph nodes, and mediastinum were detected. Since 2016, the patient has been under observation for chronic lymphocytic leukemia.

At the time of discharge, an echocardiographic study (EchoCG) was conducted, and no peculiarities were identified. The laboratory data available at that time are presented in Tables 1 and 2.

Table 1. Laboratory test results from January to November 2023

Indicators	Data				Reference values
	January 10, 2023	January 11, 2023	October 17, 2023	November 05, 2023	
Hemoglobin, g/ L	91	115	103	95	130–160
Hematocrit, %	27	33.9	38.4	29.8	40–48
Erythrocytes, 10^{12}/L	3.13	4	3.56	3.32	4–5.6
Leukocytes,10^{9}/L	65.1	84.2	71.7	173.12	4–9
Lymphocytes,10^{9}/L	51.7	65.1	40	–	1.2–3
Segmented neutrophils, %	20	4	29	38.3	47–72
Eosinophils, %	5	3	29	15	0.5–5
Platelets, 10^{9}/L	161	205	160	73	180–320
ESR, mm/h	16	59	55	40	1–10

Table 2. Dynamics of high-sensitivity troponin level in blood samples

	January 10, 2023 01 hour and 51 minutes	January 10, 2023 11 hours and 13 minutes	October 17, 2023	October 18, 2023	October 18, 2023	October 31, 2023	November 11, 2023
Troponin (I) (N 0-34 ng/L)	5.7	26.8	983.1	1259.3	1510.3	1501.9	438.2

In April 2023, the patient underwent chemotherapy for carcinoma metastases using vinorelbine at 60 mg/m^2 on days 1, 8, and 21. Thereafter, the patient had no symptoms until September 2023.

In October 2023, the patient was readmitted to Saint Petersburg City Pokrovskaya Hospital because of an atypical pain in the precordial region and frequent VT paroxysms, occurring 3–4 times per day. On October 17, 2023, ECG exhibited alterations identical to those observed in the January 2023 (Fig. 1).

Considering the elevated high-sensitivity troponin levels upon admission and tendency for these levels to remain elevated, a series of diagnostic procedures were conducted on hospitalization day 1, including coronary angiography, coronary shuntography, and ventriculography.

Coronary angiography findings:

- Right type of coronary blood supply.
- Left coronary artery without stenosis.
- AIVA: condition after stenting from the orifice (2012), chronic occlusion in the stent. Periphery: filled from the CABG and right coronary artery (RCA) collaterals.
- Diagonal artery: filled by a functioning CABG and retrogradely by collaterals of the circumflex artery (CA).
- CA: main branch without stenosis.
- Marginal artery: eccentric stenosis in the proximal third not exceeding 60%.
- RCA: moderately changed in proximal and middle third; stenosis not more than 60%.

Coronary shuntography

The CABG to AIVA function was satisfactory, with no anastomosis defects. In the case of chronic occlusion of AIVA immediately after anastomosis, the shunt functions on the septal and diagonal branches that originate from more proximal segments of the artery. Additionally, the apical segment of AIVA is filled retrogradely from the RCA pool.

Ventriculography showed no focal contractility abnormalities in the left ventricle (LV) and ejection fraction > 55%.

Subsequently, high troponin levels persisted throughout the hospitalization (Table 2).

Since hospitalization day 1, recurrent episodes of VT accompanied by a decline in blood pressure were observed. The ventricular nature of the arrhythmia was unquestionable. VT was diagnosed using the criteria by Vereckei A. et al. [8]: a QRS complex type R in the aVR lead and a Vi/Vt ratio ⩽1 (Vi, rate of voltage change during the first 40 ms of the QRS complex; Vt, rate of voltage change during the last 40 ms of the QRS complex).

The initial episodes of VT were brief and self-limiting, resolving spontaneously. However, they eventually became longer in duration and necessitated the administration of ECV.

Two distinct types of VT were identified during the course of the patient's hospital stay. The morphology of the complexes in both cases was practically identical, and the shape of the QRS complexes fully coincided with the description of VT from January 2023. Specifically, the shape was that of

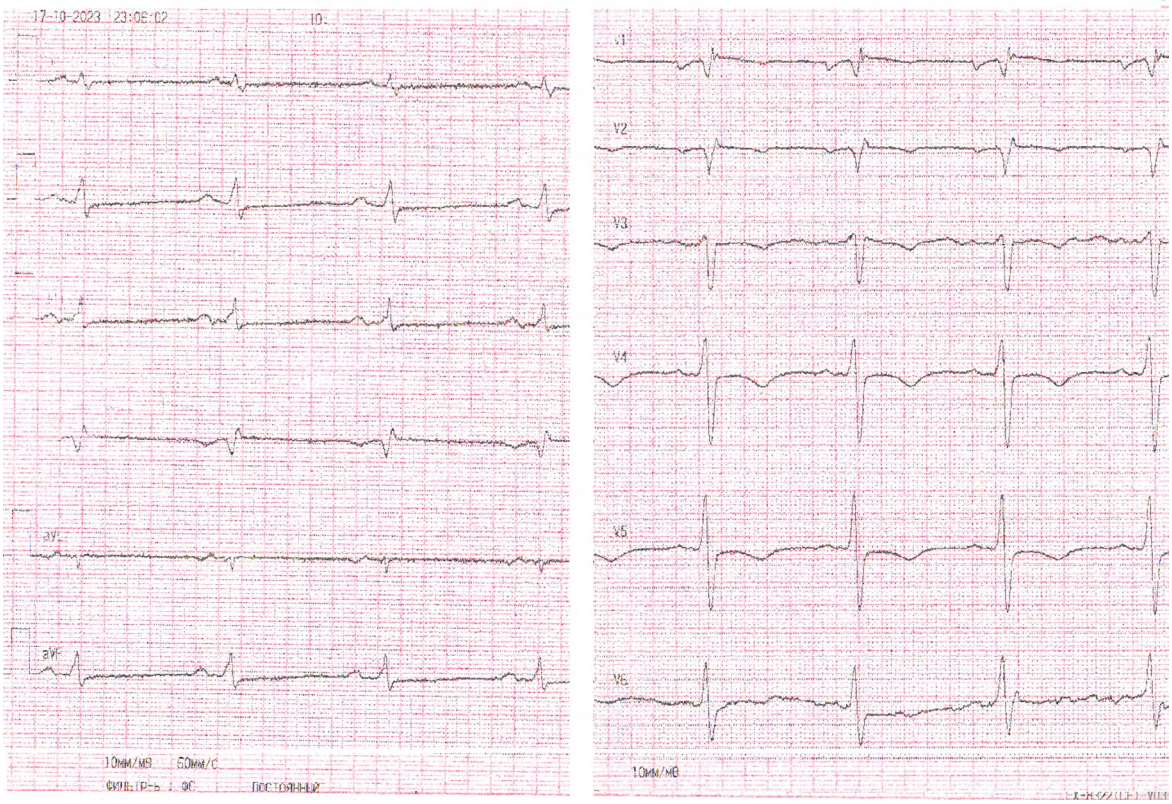


Fig. 1. ECG on October 17, 2023. Sinus rhythm with a rate of 88 per minute. Cardiac rotation of the right ventricle anteriorly and the apex posteriorly. Left atrium enlargement. Disseminated diffuse myocardial changes

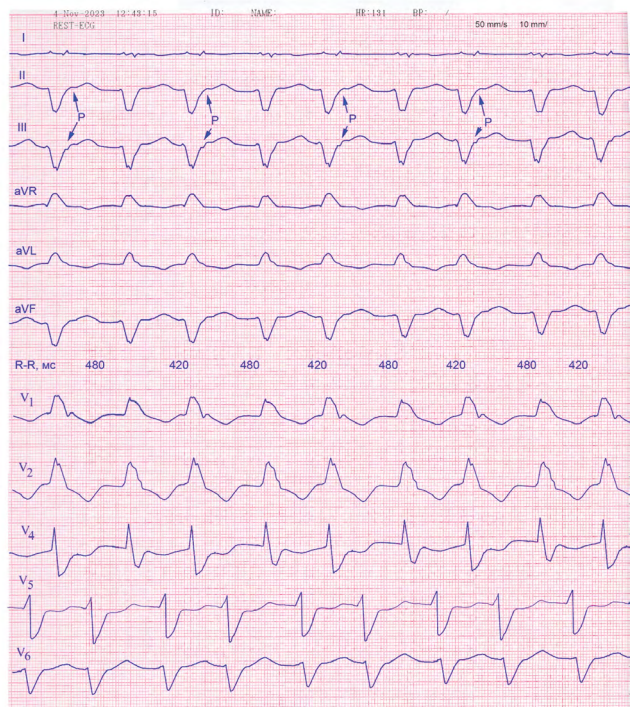


Fig. 2. ECG on November 4, 2023. Monomorphic reciprocal left ventricular tachycardia with a rate of 131 per minute. *QRS* complex is 150 ms and has the shape of a complete RBBB and LAFB, *R*-shape in a*VR* lead, and Vi/Vt ratio < 1 in V5 lead. The regular fluctuations of the *R-R* intervals can be explained by conduction through reentry loops of different sizes

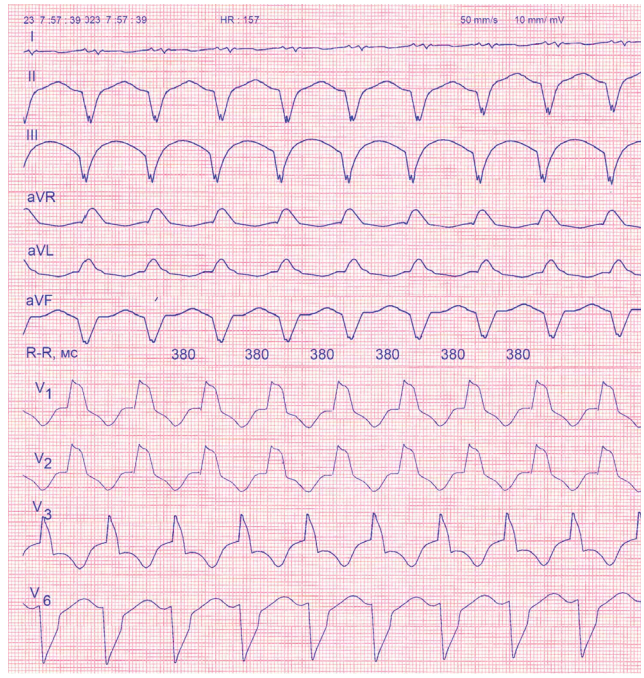


Fig. 3. ECG no. 2, November 4, 2023. Monomorphic reciprocal left ventricular tachycardia with a rate of 157 per minute. *QRS* complex is 150 ms, in the form of a complete RBBB and LAFB, *R*-shape in the a*VR* lead, and *r/S* ratio in the V6 lead < 1

a complete RBBB and LAFB with a QRS width of 150 ms. When analyzing the ECG of type 1 VT, with a frequency of 131 bpm (Fig. 2), attention was drawn to the strictly regular alternation of two identical RR intervals (420 and 480 ms) and negative oscillations in the lower leads after the short R-R interval. The first impression of duplicated VT seemed unlikely, as this variant could involve two independent ventricular sources of automaticity operating simultaneously, both at excessively low and similar frequencies (~60 and 75 bpm). The presence of reciprocal LV VT was more probable, with

two channels of impulse propagation, similar to the figure of eight configuration, in which the conduction time through one of the channels is longer than that through the other channel, with retrograde conduction of the impulses to the atria in a ratio of 2:1.

Moreover, type 2 VT recorded on the same day was strictly regular, with a frequency of 157 bpm and similar characteristics of the QRS complexes of type 1 VT, but without regular fluctuations of the *R-T* intervals (which was considered to be propagation of the impulse along a single reentry loop). Additionally, no *P*-wave could be detected.

In the intervals between hemodynamically significant VT paroxysms, frequent ventricular extrasystoles were recorded, the morphology of which was similar to the QRS complexes in the VT circuit (Fig. 4).

EchoCG showed hypercontractility of the basal and mid-LV segments associated with local akinesia of the apex (Merlon's sign) and significant wall masses,

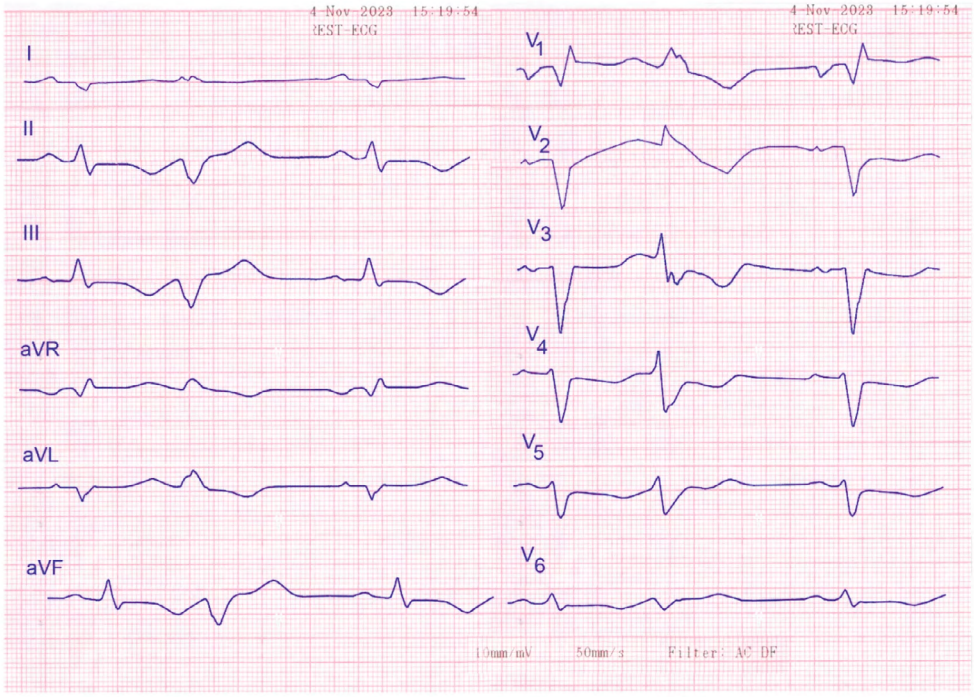


Fig 4. Sinus tachycardia ~100 per minute. Left ventricular extrasystole with complete compensatory pause, having the form of a complete RBBB and LAFB, similar to the form of *QRS* complexes in tachycardia. Overload of the left atrium

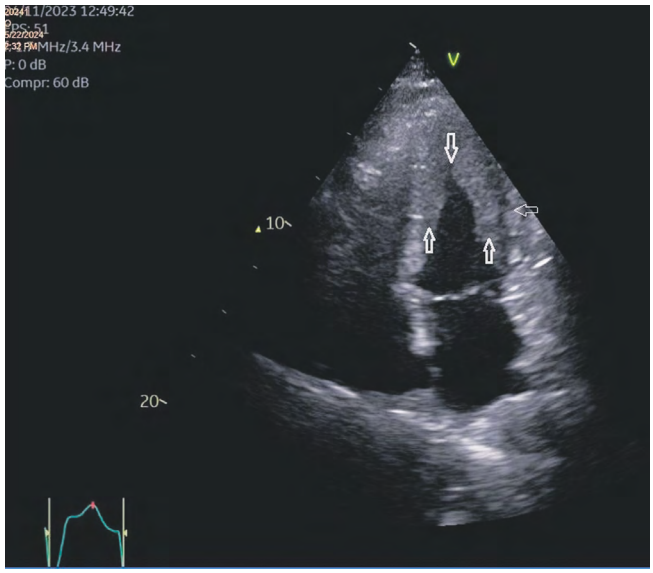


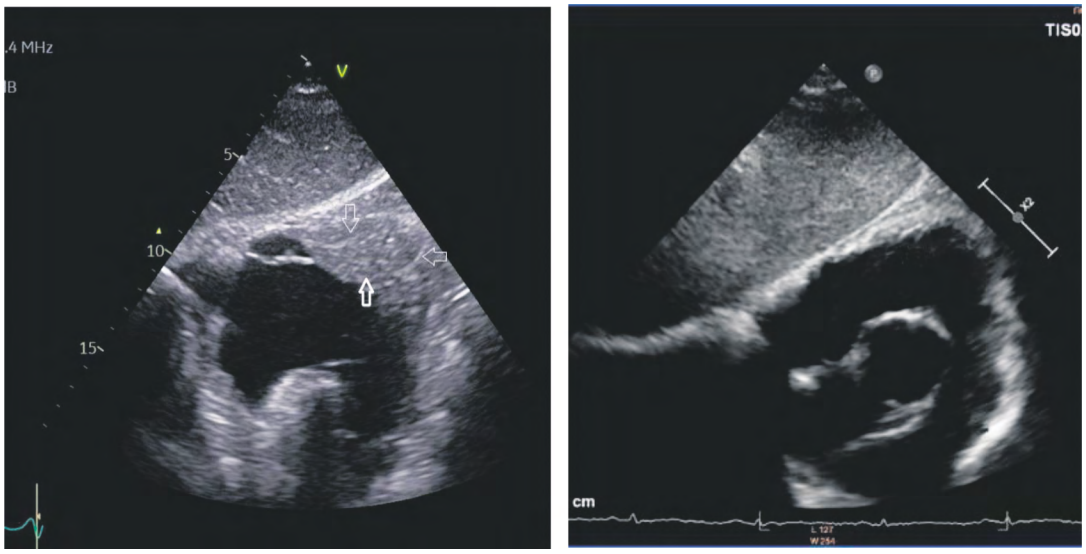
Fig. 5. Echocardiogram of Loeffler endomyocarditis of the LV. Four-chamber view, apical approach. The arrows indicate wall masses in the area of the akinetic apex and in the projection of myocardium with preserved local contractility. The border between the myocardium and myocardial projections is clearly visible. The wall masses and myocardium have different densities, and there is an obvious boundary between them. Vertical arrows indicate extensive wall masses initially believed to be thrombus; horizontal arrow indicates LV myocardium

which were initially believed to be extensive thrombotic deposits. These masses were localized in the area of the fixed apex and in the protrusion of myocardium with preserved contractility (Fig. 5). A similar condition was observed in the region of the outflow tract and the apex of the right ventricle (Fig. 6). LV systolic function was preserved. No echocardiographic evidence of severe diastolic dysfunction was noted.

Based on the echocardiographic data, Loeffler endomyocarditis was diagnosed. In the hospital, the patient received anti-inflammatory therapy with glucocorticosteroids (in doses not exceeding the dose of prednisolone of 1.0 mg/kg intravenously) and antiarrhythmic therapy with amiodarone; however, the disease progressed. On hospitalization day 22, another VT paroxysm developed into ventricular fibrillation and then to asystole. Resuscitation was unsuccessful.

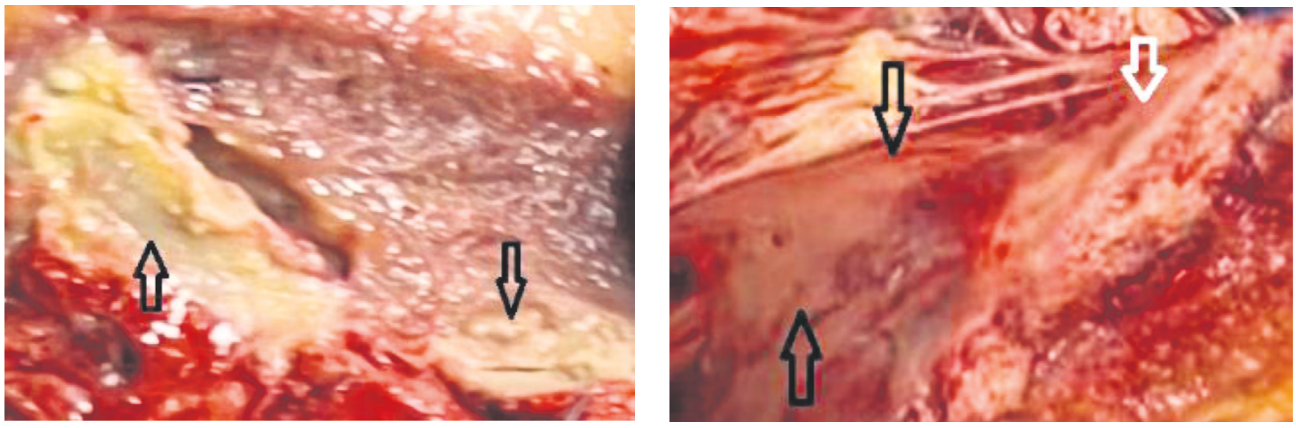
Pathologic examination confirmed the diagnosis of Loeffler endomyocarditis. Macroscopically, large areas of inflammation and marked thickening of the endocardium of the left and right ventricles, with evidence of inflammation extending into the myocardium, were found. Two adjacent foci of muscle necrosis were noted in the apical part of the LV (Fig. 7).

Clinically, no mural thrombus was found on pathologic–anatomic examination. What was believed to be a thrombotic mass in the wall was actually an inflamed, friable, and significantly thickened (edematous) endocardium.



a *b*

Fig. 6. Echocardiographic changes in the right ventricular outflow tract: *a* — short-axis view at the level of the aortic valve, subcostal approach, reveals parietal masses located in the outflow tract of the right ventricle, indicated by the lower arrow. The arrows above and to the right delineate the myocardium of the right ventricle and a clear boundary between the myocardium and the parietal deposits. For comparison; panel *b* — displays the same section from a healthy individual,demonstrating a non-thickened right ventricular myocardium absent of pathological parietal masses



a *b*

Fig. 7. Macroscopic sections in the LV apex: *a* — two adjacent foci of necrosis of pale yellow color (black arrows); *b* — thickened, inflamed endocardium of pale pink color. Intact endocardial areas are marked with black arrows and damaged areas with white arrows

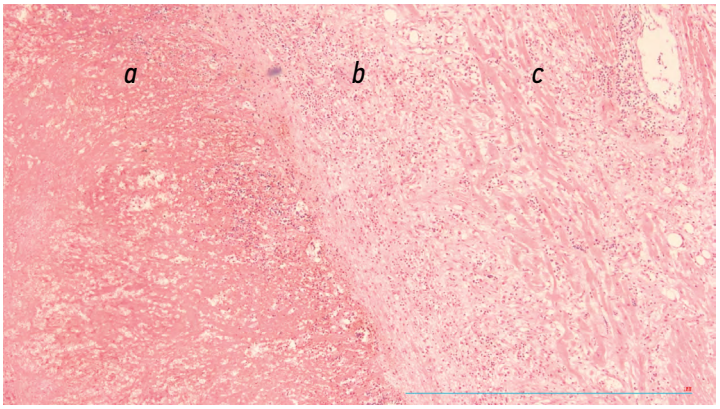


Fig. 8. Histological section of the endocardium and adjacent myocardium: *a* — endocardium; *b* — focus of necrosis; *c* — myocardium. At the border of the endocardium and myocardium, signs of necrosis of both endocardium and adjacent myocardium are noted. In the zone of endocardial necrosis, the presence of necrotic tissue, fibrin, and hemolyzed blood elements is observed. In the adjacent myocardium, similar changes are found: signs of necrosis, overgrowth of granulation tissue, and massive infiltration of the whole area with lymphocytes, plasmocytes, and eosinophils

Histological examination revealed eosinophilic infiltration of the endocardium and myocardium (Fig. 8), as well as of the liver, spleen, bone marrow, and lungs.

DISCUSSION

The course of Loeffler endomyocarditis is characterized by three distinct stages: the acute necrotic stage, stage of wall thrombus formation, and stage of endomyocardial fibrosis. The acute stage persists for approximately 5-6 weeks and lacks distinctive symptoms, although fever, sweating, and arrhythmias may be present. Manifestations of the disease become evident at a later stage, exhibiting as recurrent thromboembolic events in the second stage and progressive heart failure in the third stage.

From a clinical perspective, it is noteworthy that the initial registered manifestation of the disease in the patient was a VT that occurred 10 months prior to the onset of the principal events. Prior to this, the patient with CHD had not experienced any ventricular arrhythmias, including coronary events. VT occurred concurrently with hypereosinophilia, with an estimated eosinophil count of 3255/μL. However, the percentage of eosinophils remained within the normal range, which was probably the reason for the underestimation of hypereosinophilia. The presence of granulation tissue in histologic sections indicated that there may have been earlier foci of necrosis at this site, which were eventually replaced by fibrous tissue. On January 10, 2023, myocardial damage was demonstrated by a marked increase in troponin levels in less than 10 hours. In practice, the increase in troponin level is often associated with myocardial damage owing to electrical discharge during ECV (especially during multiple ECV). Nevertheless, currently available data do not show a definitive correlation between ECV and troponin elevation. This observation reinforces the need to identify other causes of myocardial damage. Furthermore, had troponin levels been monitored in January 2023, a further rise in troponin levels would probably have been detected. However, this remains an assumption.

In the present case, the natural organic substrate of VT was fibrotic and necrotic myocardial changes that created conditions for reentry. The most remarkable indicator of reciprocal tachycardia is the near-complete uniformity of *R-R* intervals within the tachycardia chain. Both were recorded in our patient and exhibited absolute regularity. Furthermore, in the first type of tachycardia circuit, the R-R intervals exhibit a strict alternation of 420 and 480 ms, which occurs when impulse conduction is carried out by two loops of reentry, rather than a single one. A similar character of reciprocal tachycardia was previously presented by W.G. Stevenson et al. [10].

The presented types of VT represent two hypostases of a single reciprocal tachycardia originating from the high regions of the interventricular septum (IVS), which is clinically referred to as fascicular ventricular tachycardia (FVT) or verapamil-sensitive left VT. The morphology of the complexes was similar to that in FVT. In tachycardia, a complete RBBB is present, accompanied by a leftward deviation of the electrical axis. In contrast, under sinus rhythm, no initial similar changes are evident. This point of view has been explained; however, it ignores clinical and morphological data, particularly the presence of obvious morphological changes in the apex region, which is a suitable substrate for VT, whereas no changes were found in the high IVS region [10].

The presence of two foci of necrosis and two types of tachycardia showed that two different reciprocal tachycardias have developed, despite the similar morphology of the ventricular complexes. The similarity of the QRS complexes can be explained by the fact that, according to the autopsy results, all fibrotic–necrotic changes were compactly localized in the cardiac apex or that the direction

of the vectors of electrical excitation propagation should be similar.

Clearly, our reasoning was speculative; however, assuming that it is correct and the first VT paroxysm was indeed the manifestation of LEM, no characteristic signs of LEM were detected by EchoCG at that time. Additionally, there was still no reliable diagnostically significant troponin elevation. Later, progressive hypereosinophilia developed (in the final stage, the number of eosinophils reached 23000/μL).

Remarkably, the relative stabilization of the condition (from January 2023 to September 2023) coincided with the course of chemotherapy. The main treatment method for reactive HES is effective therapy of the underlying disease [11]. Thus, our patient had no hemodynamically significant arrhythmias for 5 months after chemotherapy, and the fact that the leukocyte count at the beginning of the second hospitalization was slightly lower than in January may indicate the efficacy of the chemotherapy performed. Thus, chemotherapy may have slowed down the development of advanced clinical manifestations of LEM.

The abovementioned indicates that, in the present case, the reactive paraneoplastic LEM had a chronic wave-like character, with periods of exacerbation followed by periods of relative stabilization due to adequate therapy.

Treatment of LEM may vary depending on the type of HES. The three variants of HES should be differentiated when choosing a treatment option:

1. Primary or clonal: myeloproliferative and myelodysplastic conditions in which eosinophils represent part of a neoplastic clone and/or FIP1L1/PDGFRA mutations are present [12, 13, 14].

2. Reactive: hypereosinophilia is formed in response to exogenous stimuli via IL-3, IL-5, etc. (i.e., allergic conditions, parasitic infections, adverse drug reactions, and inflammatory or neoplastic diseases).

3. Idiopathic hypereosinophilia: after exclusion of clonal and reactive HES.

In the primary variant, treatment is based on the administration of tyrosine kinase inhibitors (primarily imatinib), whereas the first-line treatment of reactive hypereosinophilia in the absence of FIP1L1/PDGFRA mutation is glucocorticoid steroids (GCS). Evidently, the primary course of action in reactive HES should be etiologic therapy. This may involve antiparasitic treatment for worm infestations, chemotherapy for neoplasms, or drug withdrawal in cases of drug hypersensitivity. The recommended starting dose of prednisolone is 1.0 mg/kg of body weight when administered orally and 5 mg/kg when administered intravenously. In critical cases, the total dose of methylprednisolone administered over a 3-day period may reach 1,000 mg. In cases of reactive HES, it is not recommended to prolong aggressive GCS therapy for more than 3–6 months. Imatinib-sensitive mutations should be excluded, even in cases wherein reactive HES is a potential diagnosis, as clonal HES has been demonstrated to exhibit resistance to steroid therapy [13, 14].

In idiopathic HES, mepolizumab, a humanized monoclonal antibody (IgG1, kappa) directed against IL-5, is the recommended treatment [13, 14].

In the event of resistance to initial pharmacological agents, alternative treatments may be considered, including immunosuppressive drugs (e.g., imatinib, hydroxyurea, vincristine, chlorambucil, etoposide, and cytarabine), immunomodulators (e.g., peginterferon alfa-2a and interferon alfa-2b), and interleukin inhibitors (e.g., mepolizumab and benralizumab) [13, 14].

CONCLUSIONS

The main diagnostic sign of Loeffler endomyocarditis is hypereosinophilia. A high level of physician vigilance is warranted for the recognition and differential diagnosis of hypereosinophilia and hypereosinophilic syndrome.

Ventricular rhythm disturbances with hypereosinophilia may be an early manifestation of Loeffler endomyocarditis and precede diagnostically significant troponin elevations and appearance of typical echocardiographic and electrocardiographic signs.

The use of adequate doses of GCS should be preceded by the exclusion of imatinib-sensitive mutations.

The course of reactive (in the present case, paraneoplastic) Loeffler endomyocarditis may be wavy, with periods of relative stabilization during effective therapy of the underlying disease, provided that such therapy is initiated at the early stage of endomyocarditis.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors confirm that their authorship complies with the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research, and preparation of the article, as well as read and approved the final version before its publication). Personal contribution of the authors: Yu.N. Grishkin, V.Yu. Zimina — concept, design, materials processing, data analysis, writing, literature review; P.O. Karchikian — collection, processing, analysis of echocardiographic data, literature review; A.A. Babayan — collection and analysis of daily monitoring data, literature review; O.V. Grigorieva — collection, processing, analysis of pathological and histological data; T.B. Butaev — materials processing, data analysis.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Вклад каждого автора: Ю.Н. Гришкин, В.Ю. Зимина — концепция, дизайн, обработка материалов, анализ данных, написание текста, обзор литературы; П.О. Карчикьян — сбор, обработка, анализ данных ЭхоКГ, обзор литературы; А.А. Бабаян — сбор и анализ данных суточного мониторирования, обзор литературы; О.В. Григорьева — сбор, обработка, анализ патологоанатомических и гистологических данных; Т.Б. Бутаев — обработка материалов, анализ данных.

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Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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Clinical case of successful treatment of focal ventricular arrhythmia in a patient with arrhythmogenic mitral valve prolapse

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ABSTRACT

The problem of managing of patients with mitral valve prolapse and ventricular arrhythmias — arrhythmogenic mitral valve prolapse — is quite relevant in routine clinical practice, which led to the creation in 2022 of an expert consensuses on the management of such patients. Based on the criteria, it is possible to identify a group of people at high risk of sudden cardiac death and implement measures to prevent death. How to manage patients at moderate risk of sudden cardiac death remains unclear. A clinical case of successful treatment of ventricular arrhythmias in a patient with arrhythmogenic mitral valve prolapse is presented.

Keywords: arrhythmic mitral valve prolapse; ventricular arrhythmias.

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Клинический случай успешного лечения фокусной желудочковой аритмии у пациентки с аритмогенным пролапсом митрального клапана

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АННОТАЦИЯ

Проблема ведения пациентов с пролапсом митрального клапана и желудочковыми нарушениями ритма — аритмогенным пролапсом митрального клапана — достаточно актуальна в клинической практике, что привело к появлению в 2022 году экспертного консенсуса по ведению таких больных. На основании созданных критериев можно выявить группу лиц высокого риска внезапной сердечной смерти при пролапсе митрального клапана и осуществить мероприятия по ее предотвращению. Как вести больных с умеренным риском внезапной сердечной смерти остается не до конца понятным. Предлагается клинический случай успешного лечения фокусной желудочковой аритмии у пациентки с пролапсом митрального клапана.

Ключевые слова: аритмогенный пролапс митрального клапана; желудочковые нарушения ритма.

Как цитировать

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Mitral valve prolapse (MVP) is common in the general population; it is most often detected during routine echocardiography (ECG) and has a benign course [1–3]. Most patients with MVP have no clinical manifestations; however, in some cases, individuals with MVP experience serious complications such as severe mitral regurgitation requiring surgical correction, infective endocarditis, systemic emboli, atrial fibrillation, ventricular arrhythmias (VAs), and even sudden death [4, 5]. Sudden cardiac death (SCD) occurs in 0.2%–0.4% of patients with MVP, which is higher than in the general population [3, 6, 7].

Studies on the causal relationship between MVP and SCD showed an association between myocardial electrical instability and structural changes of the mitral apparatus, such as left ventricular fibrosis in the papillary muscles and inferior basal wall, mitral annular disjunction (MAD), and systolic torsion [3, 6, 7].

In recent years, the incidence arrhythmogenic mitral valve prolapse has been reported, which is defined as MVP associated with frequent or complex VAs, including life-threatening ones (i.e., ventricular tachycardia (VT) and ventricular fibrillation (VF) in the absence of any other arrhythmic substrate [with or without MAD]) [8]. An expert consensus on the management of these patients has been published [6]. According to data from various studies, most cases of SCD occur in young healthy women with MAD [3, 7, 9]. A clinical profile of a patient with arrhythmogenic MVP was developed based on case studies presented in the literature. It includes a young or middle-aged woman with lesions in both mitral valve flaps, conduction disturbances in the His bundle branch system, repolarization disorders (*ST* segment displacement and *T* plaque inversion), and polymorphic ventricular extrasystoles with a morphology resembling a right bundle branch block [3, 7, 10, 11].

This case study presents the treatment of focal VA in a middle-aged patient with MVP.

A 54-year-old woman with complaints of heart palpitations and a freezing sensation was admitted to the cardiology clinic of the Mechnikov North-Western State Medical University on October 10, 2023. No conditions in the other organ systems were reported.

The patient's medical history indicates that she first experienced heart palpitations at the age of 30. However, at that time, an examination for rhythm disturbances was not conducted, and no arrhythmias were observed on electrocardiogram (ECG). At the same age, she began to have elevated blood pressure up to 160/90 mmHg, which was subsequently treated with hypotensive medication (ACE inhibitor + Ca-antagonist), resulting in a favorable outcome. Moreover, her total cholesterol levels gradually increased up to 6.6 mmol/L (with triglyceride levels at 1.2 mmol/L, HDL-C at 1.84 mmol/L, LDL-C at 4.21 mmol/L, and an atherogenicity coefficient of 2.6) over an extended period. However, no hypolipidemic therapy was prescribed.

The initial 24-hour ECG monitoring was conducted on March 17, 2020, in the absence of pharmacological intervention. Sinus rhythm with heart rate (HR) ranging 58–140 beats per minute (bpm), with a mean HR of 86 bpm, was noted. Submaximal HR was achieved. The number of type 1 single ventricular extrasystoles was 332 (15 per hour), whereas the number of type 2 single ventricular extrasystoles was 91 (4 per hour). Additionally, seven paired ventricular monomorphic extrasystoles were found. The number of single supraventricular extrasystoles was 114 (5 per hour). No ischemic changes were observed. The patient was prescribed 5 mg of bisoprolol by a cardiologist at her place of residence.

Four months later, a control 24-hour ECG monitoring was performed in conjunction with therapy. The patient exhibited a sinus rhythm with HR ranging 58–138 bpm (average HR: 78 bpm). Additionally, she demonstrated submaximal HR and type 1 single ventricular extrasystoles at a rate of 122 per hour (5 per minute), type 2 single ventricular extrasystoles at a rate of 31 per hour (1 per minute), and single supraventricular extrasystoles at a rate of 79 per hour (3 per minute). ECG revealed no ischemic changes. Considering the favorable clinical response to β-blockers, the patient was instructed to continue therapy.

In 2021 (after experiencing severe stress and the effects of the novel coronavirus), the patient reported increase in the frequency of attacks, which occurred several times a week. These attacks manifested as a sensation of heart palpitations during periods of physical exertion and at rest. The patient described this sensation as "as if everything is tumbling inside." Moreover, during these attacks, the patient experienced dyspnea. Furthermore, two episodes of presyncope were observed, occurring during complete well-being and at rest, accompanied by a sensation of heart palpitations.

A 24-hour ECG was conducted on November 9, 2022; the results are presented in Figure 1. The sinus rhythm exhibited HR ranging 55–136 bpm (average HR: 76 bpm). The frequency of type 1 single ventricular extrasystoles was 19,361 (805 per hour), whereas the frequency of type 2 single ventricular extrasystoles was 1,067 (44 per hour). Additionally, the frequency of paired ventricular monomorphic extrasystoles was 1,267 (53 per hour). Paired ventricular polymorphic extrasystoles were observed at a rate of 364 per hour (15 per hour), whereas nonsustained monomorphic VT was noted at a rate of 40 per day (2 per hour) only during daytime. Similarly, nonsustained polymorphic VT was observed at a rate of 27 per hour (1 per hour) only during daytime.

The patient was initially prescribed sotalol at 120 mg per day during the outpatient phase. However, subsequent attempts to increase the dosage were associated with the development of marked bradycardia, indicating the need to maintain the previous dosage.

In conjunction with sotalol therapy, on June 27, 2023, 24-hour ECG monitoring was performed. The patient

exhibited a sinus rhythm with HR ranging 59–119 bpm (average HR: 79 bpm). Additionally, she displayed type 1 single ventricular extrasystoles, with a total of 16,553 observed over the monitoring period, representing an average of 696 per hour. The frequency of type 2 single ventricular extrasystoles was 67 instances (3 per hour); paired ventricular monomorphic extrasystoles was 982 (41 per hour); paired ventricular polymorphic extrasystoles was 135 (6 per hour) during the day, with no occurrences at night; and nonsustained VT was 34 (1 per hour) during the day, with no occurrences at night (Figure 2).

Considering the persistence of ventricular rhythm disturbances (VRD) of high degree, the patient was admitted to the Cardiology Department of the Mechnikov North-Western State Medical University for examination and determination of further treatment.

The patient's anamnesis showed that her grandmother suddenly died at the age of 42, and her father was

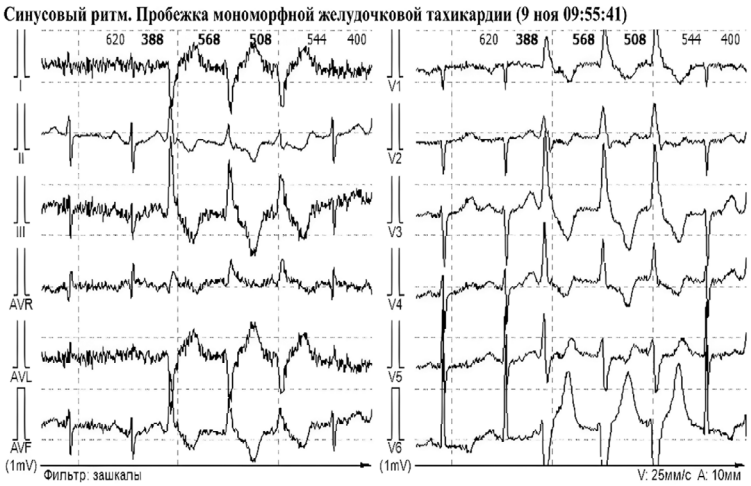

Fig. 1. Episodes of nonsustained VT according to 24-hour ECG monitoring on 11.09.2022

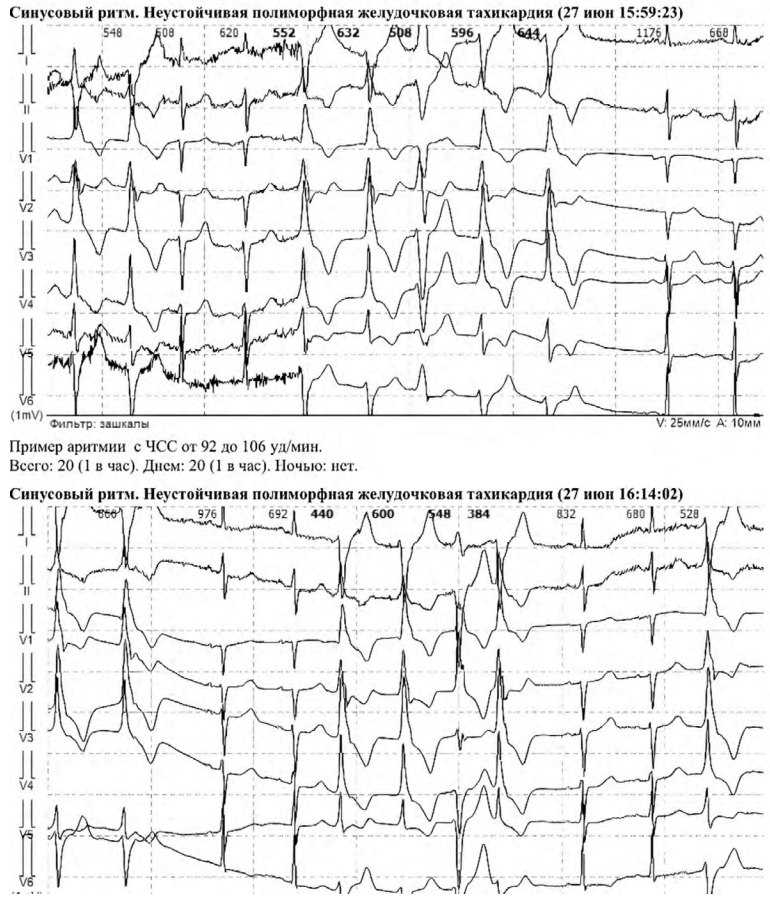

Fig. 2. Episodes of nonsustained polymorphic ventricular tachycardia according to 24-hour ECG monitoring on June 27, 2023

diagnosed with MVP and VRD, for which he was taking drug therapy (the patient found it difficult to answer). We invited the patient's father to the clinic for examination; however, he did not show up.

Since her youth, the patient has been involved in sports (athletics); she has been examined in sports clinics, and no pathology has been detected. No menstrual disorders were detected, and one pregnancy ended with medical abortion at the age of 17 (for social reasons). The patient smokes up to five cigarettes a day for 30 years.

Initial observation upon admission demonstrated that the patient's condition was satisfactory. The patient displayed clear consciousness. She weighed 56 kg, and her height was measured at 165 cm. The patient's pulse rate was 65 bpm, exhibiting an arrhythmic pattern (extrasystole). The characteristics of the pulse were satisfactory. Additionally, the boundaries of relative cardiac bluntness were not dilated. The heart tones were muffled, and no pathological murmurs were audible. The arterial pressure was 125/90 mmHg, and the chest was of the normal shape. The respiratory rate was 16 per minute, and at auscultation, breathing was rigid and conducted in all sections. No adverse respiratory noises were noted.

A series of clinical and laboratory investigations were conducted, including a comprehensive blood analysis and biochemical assessment, which did not reveal any pathological abnormalities. Examination of thyroid status showed no abnormalities.

ECG revealed a sinus rhythm, with a HR of 64 bpm. A blockade of the anterior-upper branch of the left His bundle was observed. A gradual increase in rV1–>V3 was found. Furthermore, an abnormality in the repolarization process was determined, manifesting as a biphasic, weakly positive T wave in leads V4–V6 (Figure 3).

EchoCG data, which was collected for the first time over the entire observation period, indicated that the left ventricle (LV) was not enlarged, the myocardium was not thickened, the interventricular septum was 8 mm, and the LV posterior wall was 9 mm. Additionally, no local contractility disorders were identified, and global contractility was maintained, with an LV ejection fraction of 61.2%. Myxomatous mitral valve

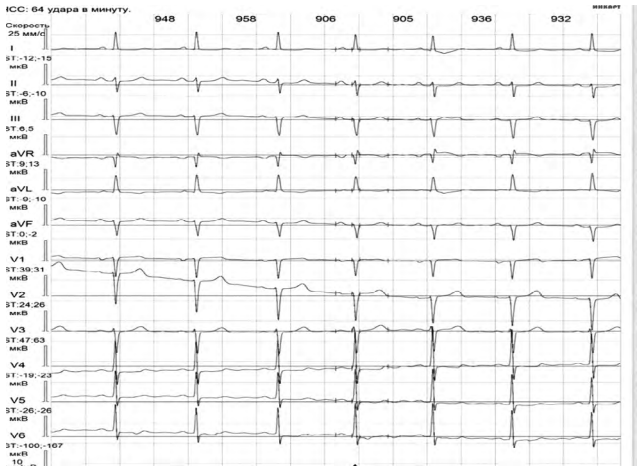

Fig. 3. Electrocardiogram on October 10, 2023

degeneration was observed, along with prolapse of both mitral valve leaflets in the second stage, with a measurement of 8 mm. Stage 1 regurgitation was observed, with a VC of 4 mm (Figure 4).

Upon analysis of the ECG and 24-hour ECG monitoring results of the patient, the localization of premature ventricular contraction in relation to the MV apparatus was not determined. This included the anterior and posterior papillary muscles and anterior and posterior sections of the mitral annulus. The ventricular complexes did not meet the existing criteria for these localizations [6]. However, the morphology of the complexes indicated that they originated from the LV.

Considering the presence of risk factors for ischemic heart disease (e.g., dyslipidemia, arterial hypertension, hereditary predisposition, and smoking), ischemic genesis of rhythm disturbances was excluded through a stress test (stress-echoCG) (with sotalol withdrawal). The results of the stress test demonstrated that the patient achieved a submaximal HR at a workload of 75 watts (equivalent to 8.40 METs). The initial examination yielded no evidence of local contractility disorders. No local contractility disorders were observed at the peak of the load. During the test, rhythm disturbances, including single and paired polymorphic extrasystoles (bigeminy), and episodes of nonsustained VT, were identified. However, the frequency of these disturbances

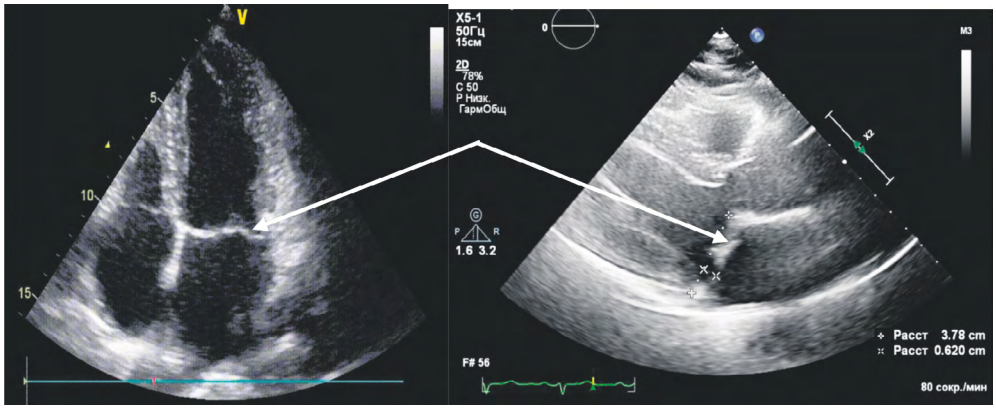

Fig. 4. Echocardiogram on 10/11/2023. Arrows show mitral valve prolapse

did not significantly increase with the increase in exercise level and HR. The pretest ECG revealed single polymorphic extrasystoles, which exhibited no significant change in frequency during exercise. In the recovery period, the degree of severity of single and paired polymorphic extrasystoles did not differ from that observed in the preload test data.

Subsequently, the patient underwent diagnostic coronary angiography, which showed that the coronary arteries were unchanged. To exclude myocarditis and identify the morphologic substrate of VRDs, myocardial magnetic resonance imaging (MRI) with contrast (gadolinium) was conducted. Cardiac MRI was performed on a tomograph with a 3T magnetic field induction, in accordance with the standard protocol, with targeted assessment of the mitral valve.

MRI data indicated that the contractile function was found to be LV ejection fraction of 61% (59%–77%), with a stroke volume of 84 mL (57–113 mL). The end-diastolic volume was recorded at 138 mL (86–166 mL), and the end-diastolic volume index was 85 mL/m^2 (56–90 mL/m^2). Additionally, the end-systolic volume was 54 mL (22–59 mL), and the end-systolic volume index was 33 ml/m^2 (14–33 ml/m^2). The myocardial mass was 139 g (72–144 g), with a mass index of 87 g (48–78 g) (normal values for age and sex are provided in parentheses). Analysis of the images obtained in Cine mode determined posterior mitral valve leaflet prolapse, whereas no indications of MAD were identified. In a series of delayed accumulation of contrast agent in the volume of 20 mL, no evidence of accumulation in the myocardium was identified. Furthermore, no data were obtained regarding inflammatory and fibrotic changes.

Owing to the ineffectiveness of antiarrhythmic therapy, radiofrequency catheter ablation (RFA) of the area of the most frequent arrhythmia was performed, as well as an extended protocol of endocardial electrophysiological study (eEPS), considering the patient's risk factors for SCD. The patient was referred to the Department of Surgical Treatment of Complex Cardiac Dysrhythmias.

The results of the eEPS indicated that, at the level of programmed stimulation, AV conduction was decremental without gaps or ECHO responses. Ultra-frequent stimulation did not induce atrial fibrillation, atrial flutter, or atrial tachycardia. In ultra-frequent stimulation from the LV apex and LV output tract, up to three extrastimuli were applied without inducing the LV. An electroanatomical map was constructed, presenting the earliest activation in the anterior septal region, closer to the LV apex, in response to LV extrasystole. In this zone, RF current with a 40 W power was applied for at least 2 minutes, resulting in the disappearance of VE.

In the postoperative period, the patient exhibited a notable enhancement in her overall well-being, accompanied by improvement of cardiac palpitations. She was discharged for outpatient treatment, with the following recommendations: atorvastatin, 40 mg per day; perindopril, 4 mg per day; amlodipine, 5 mg per day; and bisoprolol, 5 mg per day.

In February 2024, a 24-hour ECG monitoring was conducted on an outpatient basis. The patient exhibited a sinus rhythm with HR ranging 57–139 bpm (mean HR: 76 bpm). Moreover, the patient displayed type 1 single ventricular extrasystoles at a rate of 118 per hour (5 per hour), type 2 single ventricular extrasystoles at a rate of 28 per hour (1 per hour), and single supraventricular extrasystoles at a rate of 79 per hour (3 per hour). No ischemic changes were identified on ECG. The ECG monitoring data indicated that the intervention had a favorable antiarrhythmic effect.

DISCUSSION

The clinical manifestations of MVP are often determined by the severity of mitral regurgitation (MR) [4, 6], with a severe degree of which, left atrial and LV remodeling develops. In cases wherein the MR volume is insignificant and the left heart chambers are of normal size, the prognosis for MVP is

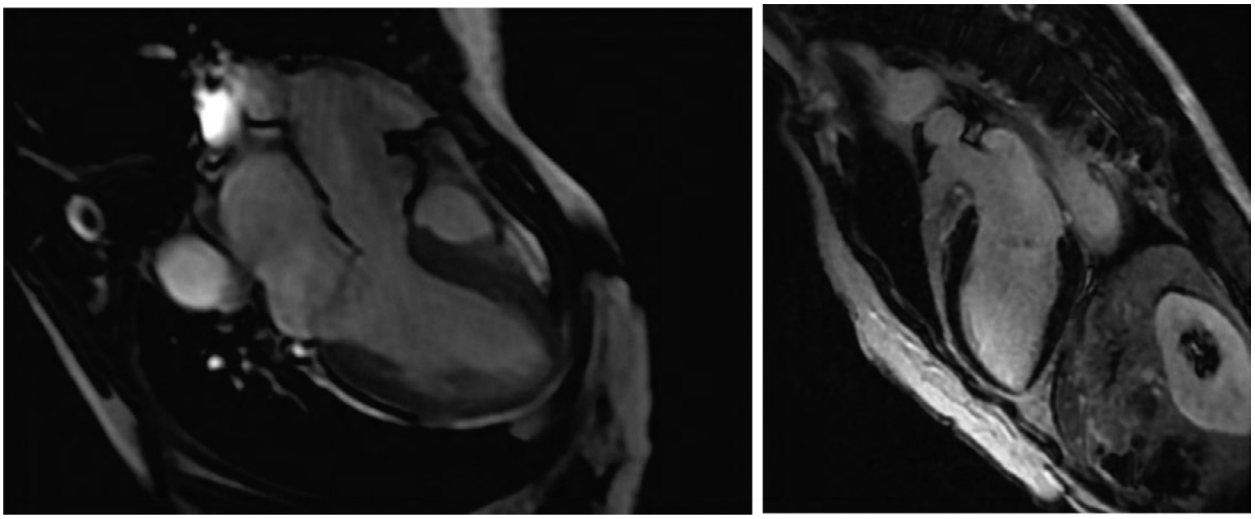

Fig. 5. Myocardial magnetic resonance imaging. Phase of delayed contrast enhancement

considered favorable [12]. Conversely, several studies have demonstrated that individuals with MVP may experience life-threatening VRDs and SCD events, irrespective of the degree of MR or LV dysfunction [9, 13, 14].

In a study by Essayagh B et al. on a large cohort of patients (n = 595) with isolated MVP, VPDs were rarely identified on 24-hour ECG monitoring. However, unstable VT, which occurred in 9% of patients and manifested as ⩾180 bpm, was identified as a predictor of SCD.

In recent years, various studies have demonstrated a significant correlation between MAD and MVP. These findings substantiate the hypothesis that a higher prevalence of MAD is evident in patients with MVP than in those with MVP and no arrhythmia [11, 15]. Conversely, evidence shows that MAD is associated with complex arrhythmic events in the absence of MVP, indicating that MAD may be considered a marker for malignant VRDs [16].

Considering the worsening of clinical symptoms and the appearance of more severe VRDs on ECG monitoring after a new coronavirus infection in 2021, our patient was assumed to have viral myocarditis. Clinical cases of increasing clinical symptoms in patients with MVP during COVID-19 have been described; however, all of them were associated with cardiac insufficiency in such patients due to acute myocarditis and increased MR without subsequent increase in VRDs [17].

In 28%–37% [18, 19] of patients with MVP, MRI shows areas of fibrosis, often localized in the annulus and papillary muscles, as well as in the inferior basal wall of the LV [20]. In our patient, cardiac MRI did not reveal severe MR and LV dysfunction, as well as MAD, signs of current or transferred myocarditis, and foci of fibrosis. This is common in idiopathic VAs. Furthermore, the occurrence of VRDs in MVP may be associated with the anatomical substrate (foci of papillary muscle fibrosis, involvement of Purkinje fibers, etc.), that is, the reentry mechanism, and with the tension of subvalvular structures with the realization of the postdepolarization mechanism [6]. Indirect indications of this condition may be the repolarization disturbances, which was observed in our patient, manifesting as biphasic, weakly positive *T* waves in leads V4–V6. Furthermore, the presence of myxomatous mitral valve abnormalities does not exclude the possibility of underlying structural pathology in other regions of the myocardium, including at the cellular level, which may not be detected through MRI.

With the absence of established protocols for patients with MVP, the standard protocol for endocardial EPS is employed in accordance with the consensus for AMVP [6]. In an independent systematic review on this topic [21], in patients with MVP who survived an episode of SCD, VT was induced in 5% of cases, supraventricular tachycardia in 23%, and FV in 18%. In 55% of cases, VRDs were not induced. Based on these findings, the authors concluded that the diagnostic value of eEPS using the standard protocol in this situation is limited.

In the present case, EPS demonstrated early activation in the anterior septal region, in proximity to the apex, concurrent with LV extrasystole. VT was not induced. Subsequent RF interaction in this area resulted in the elimination of a prevalent type of monomorphic VE, contributing to a reduction in the number of other types. The mapping data indicated the absence of focal activity from the papillary muscle structures.

Thus, despite the unproven association of the early activation zone according to eEPS data with the mitral valve area in our patient, the patient's pathology may be considered as arrhythmogenic MVP, because according to the expert consensus [6], the category of persons with AMVP includes patients with MVP (with or without MAD) with frequent (>5% of the total number of complexes) and/or polymorphic, paired VE, supraventricular tachycardia, VT, LV, and VF in the absence of other proven arrhythmogenic substrate. Furthermore, the patient exhibited characteristics of the phenotype of arrhythmogenic MVP, which was possibly of hereditary origin. She was a middle-aged woman with an asthenic physique, presenting with prolapse of two mitral valve leaflets, biphasic repolarization disorder on ECG, and polymorphic ventricular extrasystoles with right bundle branch block morphology. Additionally, ECG showed weakly positive T waves in leads V4–V6. As previously stated, the patient's father has MVP and is undergoing treatment for arrhythmias, and the patient's grandmother (on her father's side) suddenly died at the age of 42.

According to the 2022 expert consensus on the management of patients with arrhythmogenic MVP from the European Heart Rhythm Association (EHRA), high-risk patients are defined as patients with sustained VT originating from a non-right or non-LV outflow tract and those with spontaneous or unstable VT exceeding 180 bmp, syncopal states, ECG changes, SCD in close relatives, severe MR, MAD, and contrast accumulation on MRI. Our patient corresponded to the moderate risk group: polymorphic VE, unstable VT >180 bpm, frequent and paired VE, repolarization abnormalities on ECG, and history of presyncope. Therefore, arrhythmologists were requested to perform a complete eEPS.

Patients with arrhythmogenic MVP are usually prescribed the same antiarrhythmic drugs as other patients with VRDs [8, 10]. However, there are currently no studies confirming their efficacy in this pathology. According to the EHRA expert consensus [6], four treatment options are currently considered to prevent SCD in patients with arrhythmogenic MVP, namely, medical therapy, catheter ablation, ICD implantation, and mitral valve surgery. Treatment for arrhythmogenic MVP are aimed at improving symptom tolerance and survival.

Catheter ablation is an effective treatment for malignant arrhythmias in patients with MVP [10, 11, 22, 23]. F.F. Syed et al. demonstrated that RFA is feasible in patients with MVP with symptomatic, drug-resistant VAs [18].

Currently, data supporting the efficacy of cardioverter defibrillator (CD) implantation in patients at high risk for SCD in MVP are limited. Some experts recommend the use of eEPS to distinguish the risk of SCD in these patients and recommend CD implantation for primary prevention of SCD induction of sustained VT [6, 7, 15]. CD implantation in patients with arrhythmogenic MVP who have experienced cardiac arrest is performed according to the principle of secondary prevention of SCD [6, 7, 10, 11].

In our patient, antiarrhythmic drugs were ineffective, CD implantation or MR correction was not indicated, and the VRDs were symptomatic despite medical therapy. Therefore, considering the frequency and nature of the VRDs and eEPS data, an invasive intervention, namely, catheter ablation of the arrhythmogenic focus, was performed, which proved to be effective. However, the patient should be monitored by a cardiologist because MVP persists and the presence of another occult arrhythmogenic substrate cannot be excluded, as it is known that SCD develops years after the detection of VRDs in patients with AMVP [6].

CONCLUSIONS

Currently, arrhythmogenic MVP has been increasingly described. Clinical, electrocardiographic, and electrophysiological data reveal an association between MVP and SCD. Patients with mitral annular disruption are at highest risk for SCD. Moreover, malignant VAs are found in patients with MVP without MAD.

However, the mechanisms of VRDs in patients with MVP require further investigation using various more accurate methods of invasive and noninvasive mapping and the study of the cellular mechanisms of rhythm disturbances. Further search for risk markers and development of optimal evidence-based treatment strategies in these patients are warranted. General practitioners should be aware that “harmless” MVP can be fatal; thus, patients with MVP who complain of arrhythmias should undergo 24-hour ECG monitoring.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors confirm that their authorship complies with the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research, and preparation of the article, as well as read and approved the final version before its publication). Personal contribution of the authors: N.S. Tretyakova — examination of the patient, primary data obtaining, analyzing the data obtained, writing the text; S.A. Boldueva — experimental design, writing the main part of the text; making final edits; I.A. Leonova — experimental design, writing the text; literature review; O.S. Shvetsova — examination of the patient, primary data obtaining, analyzing the data obtained; L.S. Evdokimova — MRI investigation, literature review.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией. Вклад каждого автора: Н.С. Третьякова — обследование пациента, получение первичных данных, анализ полученных данных, написание текста; С.А. Болдуева — концепция и дизайн исследования, написание текста; внесение окончательной правки; И.А. Леонова — концепция и дизайн исследования, анализ литературы, написание текста; О.С. Швецова — обследование пациентки, получение первичных данных, анализ полученных данных; Л.С. Евдокимова — выполнение МРТ-исследования, обзор литературы.

Конфликт интересов. Авторы заявляют об отсутствии потенциального конфликта интересов, требующего раскрытия в данной статье.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования. Все исследования, представленные в данной статье, выполнялись в рамках рутинной клинической практики по полису обязательного медицинского страхования

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