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Reseach article

Clinical and genetic characterization of patients with catecholaminergic polymorphic ventricular tachycardia: a case series

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Abstract

AIM: of the study was to evaluate the clinical and genetic characteristics, including the development of adverse events and outcomes in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT).

MATERIALS AND METHODS: The clinical phenotype of eight patients with CPVT, two of whom were relatives of probands, was observed over 4 years. The clinical and instrumental study included ECG-12, 24-hour Holter ECG monitoring, genealogical history collection and family history of sudden cardiac death (SCD), transthoracic echocardiography and cardiac magnetic resonance imaging to detect structural myocardial changes, electrophysiologic study according to indications, and ICD monitoring. 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 8 patients, nucleotide variants of pathogenicity classes III-V were identified according to the ACMG (2015) criteria in the *RYR2* gene associated with CPVT. Pathogenic (IV-V class) and likely pathogenic (IV class) mutations in the *RYR2* gene were found in 6 (75%) probands, variants with uncertain clinical significance (VUS, class III) were found in 2 patients. At the time of diagnosis, transient QTc interval prolongation of more than 480 ms was detected in 4 (50%) patients; bradycardia less than 54 beats/min — in 2 (25%) patients, sequences of supraventricular tachycardia and ventricular tachyarrhythmia — in 2 (25%) patients. The most severe form of the disease with marked clinical manifestations and an episode of clinical death with subsequent resuscitation, as well as a transient QTc interval prolongation exceeding 500 ms was observed in patients with mutations c.11814C > A (p.Ser3938Arg, rs794728704); c.463G > A (p.Gly155Arg) and c.14876G > A (p.Arg4959Gln, rs794728811) in the *RYR2* gene. Three (37.5%) patients underwent ICD implantation; one for primary SCD prevention and two for secondary prevention.

CONCLUSION: In this study, the spectrum of clinical manifestations in patients with genetically confirmed CPVT was examined. The findings highlight transient QTc interval extensions, significant sinus bradycardia, and sequences of supraventricular tachyarrhythmias, which can escalate into life-threatening ventricular tachyarrhythmias in CPVT patients.

Keywords: catecholaminergic polymorphic ventricular tachycardia; *RYR2* gene mutation; phenotypic diversity.

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Научная статья

Клиническая и генетическая характеристика пациентов с катехоламинергической полиморфной желудочковой тахикардией (серия случаев)

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Аннотация

Цель исследования — оценить клиническую и генетическую характеристику, включая развитие неблагоприятных событий и исходов у пациентов с катехоламинергической полиморфной желудочковой тахикардией (КПЖТ).

Материалы и методы. Обследовано 8 пациентов с КПЖТ, двое из которых были родственниками пробандов, наблюдаемых в течение 4 лет. Клинико-инструментальное исследование включало регистрацию электрокардиограммы в 12 отведениях, суточное электрокардиографическое мониторирование, сбор генеалогического анамнеза и выявление случаев внезапной сердечной смерти в семье или наличия семейной формы заболевания, эхокардиографическое исследование и магнитно-резонансную томографию сердца для исключения структурных изменений миокарда, проведение эндокардиального электрофизиологического исследования по показаниям, мониторинг имплантируемого кардиовертера-дефибриллятора. Поиск мутаций в кодирующих последовательностях генов, ассоциированных с развитием каналопатий и других наследственных нарушений ритма, проводили методом высокопроизводительного секвенирования.

Результаты. У 8 пациентов выявлены нуклеотидные варианты III–V классов патогенности согласно критериям ACMG (2015) в гене *RYR2*, ассоциированным с КПЖТ. У 6 (75 %) пробандов обнаружены диагностически значимые мутации (IV–V класса патогенности) в гене *RYR2*, у 2 пациентов были обнаружены варианты с неопределенной клинической значимостью (VUS, III класс). На момент постановки диагноза транзиторное удлинение интервала *QTc* более 480 мс было выявлено у 4 (50 %) пациентов; брадикардия менее 54 уд/мин — у 2 (25 %), суправентрикулярная тахикардия, которая сменялась желудочковой тахиаритмией — у 2 (25 %) пациентов. Наиболее тяжелая форма заболевания с выраженными клиническими проявлениями и эпизодом клинической смерти с последующими реанимационными мероприятиями, а также транзиторным удлинением интервала *QTc*, превышающим 500 мс, наблюдалось у пациентов с мутациями c.11814C > A (p.Ser3938Arg, rs794728704); c.463G > A (p.Gly155Arg) и c.14876G > A (p.Arg4959Gln, rs794728811) в гене *RYR2*. Имплантация кардиовертера-дефибриллятора потребовалась 3 (37,5 %) пациентам, в том числе 1 пациенту с целью первичной профилактики ВСС и 2 (25 %) — с целью вторичной профилактики.

Заключение. В настоящем исследовании изучен спектр клинических проявлений у пациентов с генетически подтвержденной КПЖТ. Транзиторное удлинение интервала *QTc*, выраженная синусовая брадикардия и суправентрикулярная тахиаритмия, сменяющиеся жизнеугрожающей желудочковой тахиаритмией с высокой частотой представлены у пациентов с КПЖТ.

Ключевые слова: катехоламинергическая полиморфная желудочковая тахикардия; мутации в гене *RYR2*; фенотипическое разнообразие.

Как цитировать

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ЭКО•ВЕКТОР

INTRODUCTION

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmic disorder characterized by bidirectional and/or polymorphic VT induced by physical or emotional stress [1]. In the absence of optimal therapy, the mortality rate of CPVT is extremely high, reaching 30%–50% by the age of 30 years [2]. The prevalence of CPVT is reported to be as high as 1:10,000; however, its true value remains unclear [3].

The molecular genetic cause of CPVT is a defect in the *RYR2* gene, located at 1q42, which encodes the cardiomyocyte ryanodine receptor 2, a major channel for calcium release from the sarcoplasmic reticulum (SR) [4]. *RYR2* gain-of-function mutations cause abnormal calcium release from the SR, resulting in delayed depolarization and ventricular arrhythmias observed in CPVT [5, 6]. In individuals with this pathology, 65% had mutations in the gene encoding the ryanodine receptor 2, which led to the development of CPVT type 1 (CPVT1). More recently, two studies have reported consanguineous families with CPVT whose members had homozygous missense and nonsense mutations in *CASQ2*, which encodes the SR-located Ca^{2+}-binding protein calsequestrin 2. CPVT caused by *CASQ2* mutations belongs to CPVT2, is characterized by autosomal recessive inheritance, and is much less common than CPVT1 [7, 8].

The main clinical manifestations of CPVT include syncope provoked by exercise, emotional stress, or administration of beta-adrenergic drugs. Noteworthily, approximately 30% of patients with CPVT were misdiagnosed with long *QT* syndrome (*LQTS*) by reason of the presence of transient *QT* prolongation > 460 ms [9].

The symptoms of CPVT with *QT* prolongation and *LQTS*, particularly with *LQTS* type 1, are similar in that physical activity causes ventricular arrhythmias that can result in sudden cardiac death (SCD). Accurate diagnosis is crucial for the reason that the incidence of arrhythmic events during beta-blocker therapy remains significantly higher in patients with CPVT than in those with LQTS [10]. Arrhythmias develop in patients with CPVT due to delayed depolarization caused by the large amounts of calcium released from the sarcoplasmic reticulum (SR), whereas patients with LQTS develop torsades de pointes (pirouette-type tachycardias) due to increased early post-depolarization and greater heterogeneity of monophasic duration between different myocardial sites resulting from impaired functioning of predominantly potassium channels.

Remarkably, sinus bradycardia, which is occasionally observed in patients with CPVT, may be another primary disorder caused by mutations associated with CPVT [11]. Moreover, sinus node dysfunction may paradoxically contribute to the initiation of ventricular rhythm disorders and may be therapeutically targeted to prevent exercise — or stress-induced ventricular arrhythmias in CPVT [12].

Patients with CPVT usually have a normal electrocardiogram (ECG) at rest. Nonetheless, the presence of sinus bradycardia in addition to a history of exercise- or emotion-induced cardiac symptoms may be critical to the diagnosis of CPVT before exercise testing [13]. Sinus bradycardia was reported in 5%–20% of patients who were carriers of a pathogenic *RYR2* mutation and who were identified by cascade screening (testing relatives for the presence of the mutation identified in the proband) [14]. Furthermore, supraventricular rhythm disorders other than sinus bradycardia (intermittent ectopic atrial rhythm, undefined supraventricular tachycardia (SVT), and sick sinus syndrome) were found in 16% of the total population (bradyarrhythmias in 11.3% and tachyarrhythmias in 4.7%) and 38% of those on Holter monitoring. Electrophysiological cardiac studies have confirmed that sinus node dysfunction is present in at least a subpopulation of patients with CPVT [15].

Several authors noted a polymorphism of rhythm disorders characteristic of patients with CPVT, including supraventricular and ventricular arrhythmias due to significant instability and the high proarrhythmogenic potential of the myocardium at all levels (both atrial and ventricular). Currently, CPVT is recognized as one of the major causes of SCD in young adults because of the high incidence of life-threatening arrhythmias.

This study aimed to present genetic and phenotypic characterization of probands and their family members for further evaluation of clinical features, including the development of adverse events and outcomes.

MATERIAL AND METHODS

Between 2019 and 2023, 8 patients diagnosed with CPVT (4 men and 4 women, median age 34 [31–41] years) from 6 unrelated families were followed up at the Republican Scientific and Practical Center "Cardiology."

Patients underwent regular inpatient examinations at least once a year (ECG–12, 24-hour Holter monitoring, implantable cardioverter defibrillator [ICD] monitoring), endocardial electrophysiological study (EEPS) as indicated, and collection of genealogical anamnesis with ECG evaluation of all family members in order to identify SCD cases or the presence of a familial disease. Structural myocardial abnormalities were excluded by echocardiographic study with the device IE-33 (Philips, USA) according to current recommendations [16].

Arrhythmic events were defined as the occurrence of syncope, sudden circulatory arrest, appropriate ICD therapy, and SCD. The control of arrhythmic events was assessed by ECG dynamics, 24-hour Holter monitoring,

and ICD monitoring throughout the follow-up period. ECG was performed on the Intekard-3 hardware–software complex (Republic of Belarus) by computer processing. ECG was monitored over 24 hours with the Oxford Medilog AR12 recorder (UK). ECG and 24-hour Holter monitoring were evaluated according to the classic standards of ECG diagnosis. ICD activation in response to the development of life-threatening ventricular arrhythmias — sustained pirouette-type VT or ventricular fibrillation (VF) — was considered appropriate. When an ICD was triggered for atrial fibrillation (AF) or other supraventricular arrhythmias, therapy was considered inappropriate. Supraventricular arrhythmias were defined as the presence of one and/or more of the following arrhythmias: atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, atrial fibrillation, and atrial flutter.

During diagnosis, all patients were prescribed beta-blockers: the drug of choice was propranolol at a dose of 40–80 mg in 2–3 doses, with a maximum dose of 320 mg/day. If ventricular arrhythmias were registered, propranolol was administered in maximum tolerated doses, and anamnesis of arrhythmic events was positive, drug therapy was continued with nadolol at a dose of at least 120–160 mg/day. If episodes of SVT were recorded in patients taking propranolol or nadolol, an antiarrhythmic drug of class IC or III was added to the basic antiarrhythmic therapy.

All probands underwent molecular genetic testing to verify the diagnosis and determine SCD risk. Mutations in the coding sequences of 174 genes associated with cardiovascular pathology, including CPVT, were searched by high-throughput sequencing on the NextSeq 550 Gene Analyzer (Illumina, USA) using the TruSight™ Cardio Panel (USA). The pathogenicity of new and previously described genetic variants was interpreted according to the 2015 recommendations of the American College of Medical Genetics and Genomics (ACMG) [17]. Pathogenic (class V), and likely pathogenic (class IV) genetic variants were considered clinically significant. Variants of uncertain clinical significance (VUS, class III pathogenicity) in genes associated with inherited arrhythmia were analyzed separately.

If pathogenicity class IV and V mutations were detected in the proband, the disclosed variant was confirmed by Sanger sequencing and cascade screening of the closest relatives.

RESULTS

Eight patients (4 men and 4 women) diagnosed with CPVT were followed up. Two of the patients were relatives of the probands. The median follow-up period (*Me* [*LQ; UQ*]) was 16 [9; 42] months.

Genotyping of patients revealed nucleotide sequence variants in *RYR2* of pathogenicity classes III–V according to the ACMG (2015) criteria: six class IV and V mutations and two VUS (class III) (Table 1).

In most cases (5 of 8 patients), more than 1 year had elapsed between manifestation and diagnosis. A familial disease form was present in 2 out of 6 probands (33.3%). Recurrent syncope episodes were registered in 3 (37.5 %) patients. At the time of diagnosis, bradycardia of < 54 beats per minute (bpm) was noted in 2 (25%) patients, and transient QT interval prolongation of > 480 ms was registered in 4 (50%) patients (Table 1).

By way of illustration, a 32-year-old female patient (mother of proband 13m) and her 8-year-old son (13m) had identical clinical manifestations, namely, syncope, short episodes of non-sustained VT with bradycardia, and episodes of exercise-unrelated transient *QTc* prolongation. The 8-year-old boy suddenly went into cardiac arrest with VF after emotional stress. Despite prolonged resuscitation and repeated cardioversions, clinical death was declared.

In the analysis of a series of ECGs available in the patient's outpatient chart, one of the 12-lead ECGs with sinus bradycardia at a heart rate of 54 bpm showed *QT* interval prolongation > 600 ms, repolarization abnormalities in the inferolateral leads, and T-pattern changes in leads V1–V2 (Fig. 1).

24-hour Holter ECG monitoring revealed premature ventricular contractions and episodes of non-sustained polymorphic VT (Fig. 2).

Genetic analysis of the proband revealed class IV likely pathogenic variant c.11814C > A (p.Ser3938Arg, rs794728704) in a heterozygous state in *RYR2* (Table 1).

The proband's mother experienced an increase in syncope episodes 13 months after her son's death. 24-hour Holter monitoring revealed polymorphic premature ventricular contractions (306 PVCs /day), PVC couplet, ventricular bigeminy, and 11 episodes of non-sustained polymorphic VT with an average heart rate of 170–179 bpm (Fig. 3). During wakefulness and sleep, 69 episodes of pathological *QTc* prolongation (⩾ 500 ms) with a total duration of 11 h 10 min (38 episodes during wakefulness and 31 episodes during night sleep) were recorded. The patient was prescribed the beta-blocker propranolol 40 mg ½ tablet three times/day; however, PVCs and episodes of non-sustained polymorphic VT persisted. The patient was tentatively diagnosed with transient LQTS based on clinical findings (SCD of her 8-year-old son and history of syncope), *QTc* prolongation of up to 600 ms on manual assessment of 24-hour Holter monitoring, and frequent episodes of non-sustained polymorphic VT. The Schwartz scale for LQTS was 5.0. An ICD was implanted for the primary prevention of SCD due to a high likelihood of recurrent arrhythmias. Appropriate ICD therapy during waking hours was recorded during regular follow-up visits.

Genetic testing of the mother revealed the same c.11814C > A mutation (p.Ser3938Arg, rs794728704) in a heterozygous state in *RYR2* as in the son. The diagnosis was altered, CPVT was established with transient abnormally prolonged *QT* and syncope episodes based on genotyping data, and ICD implantation was performed.

In a 28-year-old proband (code 763c) with recurrent syncope episodes, ECG-12 revealed marked sinus bradycardia with a heart rate of 45–50 bpm and QT prolongation up to 500 ms. 24-hour Holter monitoring revealed frequent PVCs (extrasystole index, 4.6%). The patient was prescribed propranolol at a dose of 40 mg three times a day and a pacemaker was implanted. Eight years later, the patient suffered from pacemaker lead infective endocarditis with a thrombus in the right atrium. The disease course was complicated by the development of a pulmonary

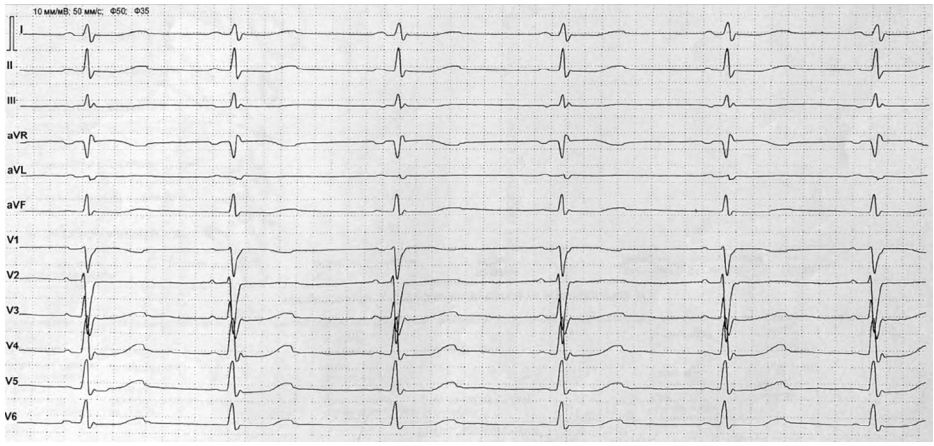
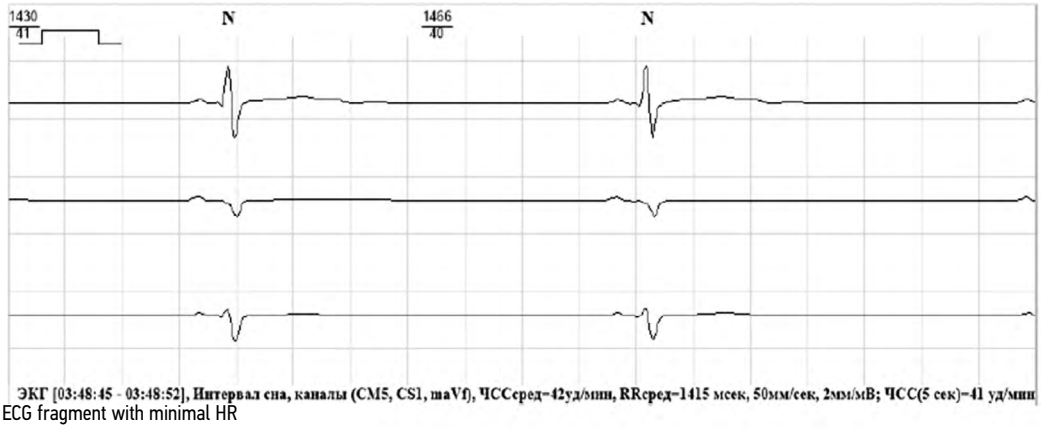
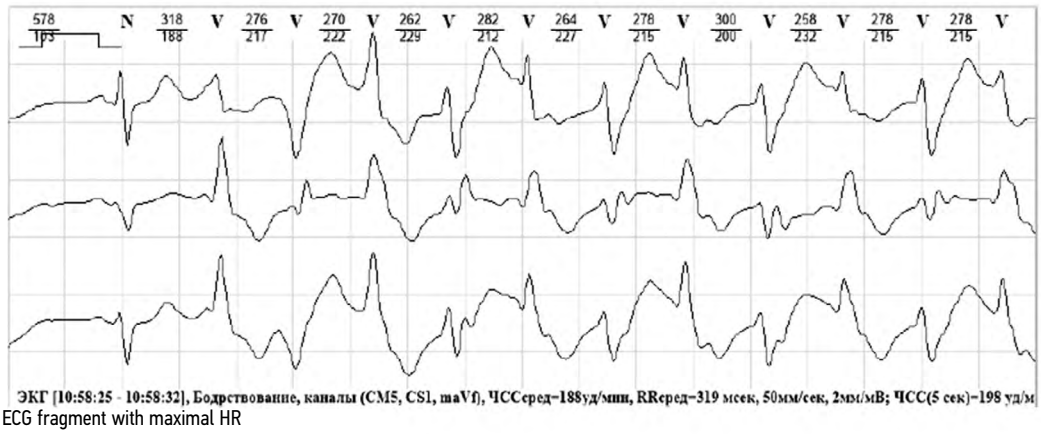


Fig. 1. Proband's 13m ECG-12
Рис. 1. Электрокрадиограмма в 12 отведениях пробанда 13м



ECG fragment with minimal HR



ECG fragment with maximal HR

Fig. 2. 24-hour holter monitoring of proband 13m ECG. Leads V5, II and aVF. ECG fragments with episodes of QTc prolongation up to 580 ms and nonsustained paroxysm of bidirectional VT
Рис. 2. Суточное мониторирование ЭКГ пробанда 13м. Отведения V5, II и aVF. Фрагменты ЭКГ с эпизодами удлинения *QTc* до 580 мс и неустойчивым пароксизмом двунаправленной ЖТ

Table 1. Clinical characterization of patients with mutations in the *RYR2* gene
Таблица 1. Клиническая характеристика пациентов с мутациями в гене *RYR2*

Patient code	Gender	Birth year	AC (amino acid) replacement, ID (dbSNP)	Pathogenicity class	Initial symptoms	Ventricular tachyarrhythmias	Atrial tachyarrhythmias	*QTc* interval, ms	EEPS with adrenergic stimulation, RFA	Therapy	Outcome
642s	Male	1996	p.Arg4959Gln, rs794728811	V	–	VF	–	500	–	Propranolol, ICD	Successful CPR, still on follow-up
Mother of 642s	Female	1978	p.Arg4959Gln, rs794728811	V	Asymptomatic	–	–	340	–	–	Asymptomatic, still on follow-up
13m	Male	2012	p.Ser3938Arg, rs794728704	IV	Frequent syncope episodes	Polymorphic VT/VF	–	600	–	–	Death
Mother of 13m	Female	1989	p.Ser3938Arg, rs794728704	IV	Frequent syncope episodes	Frequent PVCs polymorphic VT	–	500	–	Propranolol, ICD	Still on follow-up
763s	Female	1987	p.Gly155Arg, –	V	Frequent syncope episodes, bradycardia (heart rate, 45–48 bpm)	Frequent PVCs	–	500	EEPS (non-sustained paroxysm of VT was triggered)	Propranolol, pacemaker, ICD	Pacemaker lead infective endocarditis thrombus in the RA. PE
766s	Female	1989	p.Arg1086Ter, rs371303783	IV	–	Monomorphic VT	AVNRT with a heart rate of 170 bpm	350	EEPS RFA of slow-pathway AVNRT	Propranolol, propafenone, implantable loop recorder	Still on follow-up
833s	Male	1983	p.Thr1425Ala, rs776046135	VUS	–	Monomorphic sustained VT, polymorphic VT, VF	–	340	–	Propranolol	Still on follow-up
765s	Male	1877	p.Gly4315Glu, rs766109950	VUS	–	Sustained VT, polymorphic VT	Atrial flutter, AF	360	EEPS RFA of cavotricuspid isthmus. PV-cryo. RFA of VT	Propranolol, amiodarone, implantable loop recorder	Still on follow-up

Note: AC — amino acid; AF — atrial fibrillation; AVNRT — atrioventricular nodal reentrant tachycardia; CPR — cardiopulmonary resuscitation; EEPS — endocardial electrophysiologic study; ICD — implantable cardioverter defibrillator; PE — pulmonary artery thrombo embolism; PV-cryo — cryoballoon pulmonary vein isolation; RA — right atrium; RFA — radiofrequency ablation; PVCs — premature ventricular contractions; VF — ventricular fibrillation; VT — ventricular tachycardia.

Примечание: АК — аминокислота; ЭЭФИ — эндокардиальное электрофизиологическое исследование; РЧА — радиочастотная аблация; ФЖ — фибрилляция желудочков; ИКД — имплантируемый кардиовертер-дефибриллятор; СЛР — сердечно-легочная реанимация; ЖЭС — желудочковая экстрасистолия; ЖТ — желудочковая тахикардия; ЭКС — электрокардиостимулятор; ПП — правое предсердие; ТЭЛА — тромбоэмболия легочной артерии; ЧСС — частота сердечных сокращений; АВУРТ — атриовентрикулярная узловая реципрокная тахикардия; ТП — трепетание предсердий; ФП — фибрилляция предсердий; УЛВ — устья легочных вен.

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embolism. Therefore, pacemaker lead extraction procedure and a 3D-modeled pulmonary artery thrombectomy were performed.

The genetic analysis a class V pathogenic variant c.463G > A (p.Gly155Arg) in a heterozygous state in *RYR2*, and the diagnosis was altered to CPVT. Despite medical treatment (propranolol at a dose of 160 mg), the patient had frequent PVCs and episodes of non-sustained polymorphic VT. During EEPS, a polymorphic VT paroxysm was provoked, and an ICD implantation was decided.

In one patient (code 642c), the disease manifested at the age of 15 years with the development of cardiovascular arrest and polymorphic VT/VF (Fig. 4), resuscitation was successful, and an ICD was implanted for the secondary prevention of SCD. In a series of ECGs preceding the arrhythmic event, *QT* prolongation of up to 500 ms was recorded. Genotyping revealed a pathogenic *RYR2* mutation c.14876G > A (p.Arg4959Gln, rs794728811). Based on the genotyping results, the patient was diagnosed with CPVT. The proband's mother had the same mutation, with clinical manifestations characterized by presyncope episodes and palpitations. Episodes of non-sustained VT were recorded during 24-hour Holter monitoring. Medical treatment (propranolol at a dose of 40 mg in 2–3 doses) was prescribed.

Episodes of SVT were reported in two patients (765c and 766c [25%]). Patient 765c was diagnosed with paroxysmal AF and atrial flutter and underwent EEPS, cryoballoon pulmonary vein isolation (PV-cryo), and radiofrequency ablation (RFA) of the inferior vena cava-tricuspid isthmus. Patient 766c was diagnosed with paroxysmal

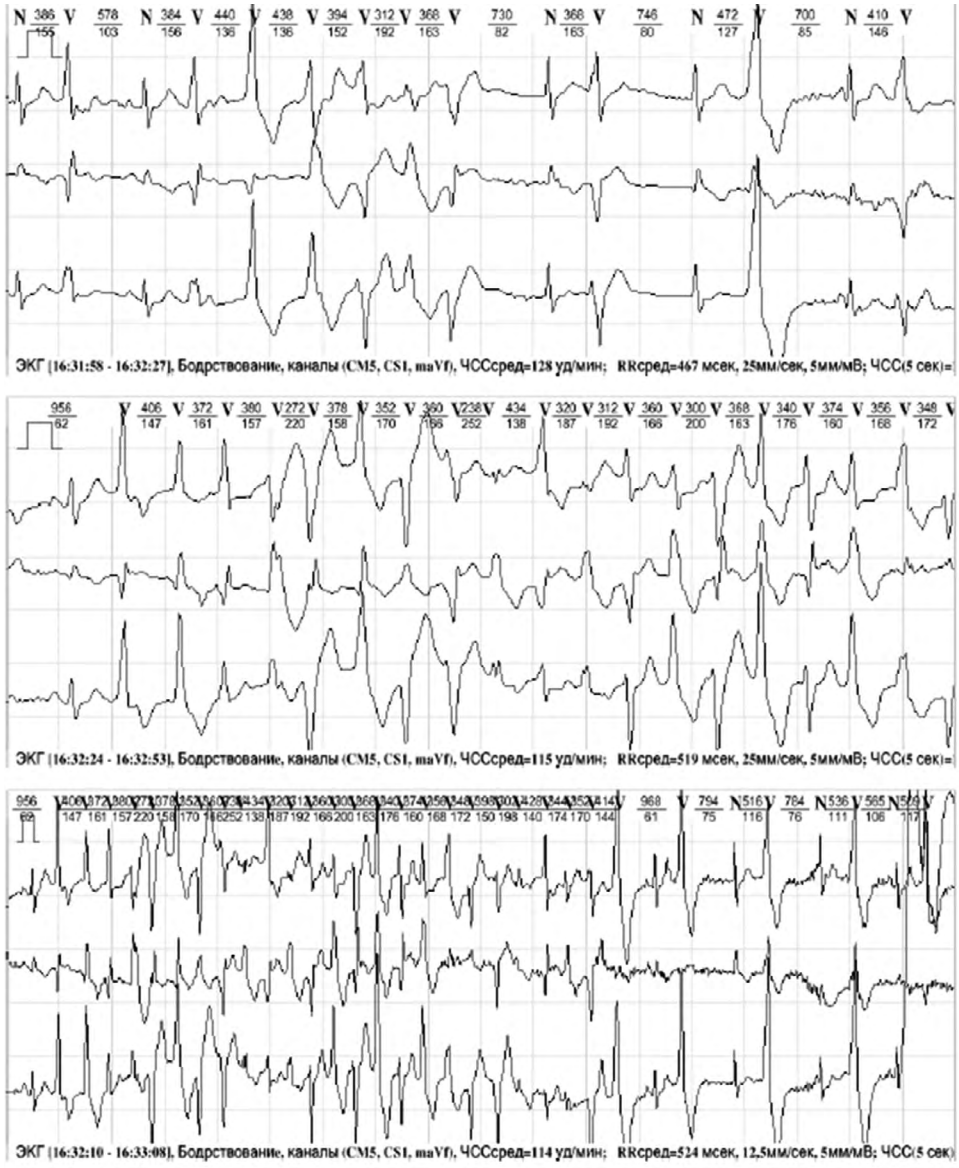

Fig. 3. 24-hour Holter monitoring of proband's 13m mother. Leads V5, II and aVF. ECG fragments with polymorphic PVCs and nonsustained VT paroxysm

Рис. 3. Суточное мониторирование ЭКГ матери пробанда 13м. Отведения V5, II и aVF. Фрагменты ЭКГ с полиморфной ЖЭС и неустойчивым пароксизмом ЖТ

atrioventricular nodal reentry tachycardia (AVNRT) and underwent EEPS and RFA of the slow pathways of the AV node. Genotyping of patients identified class III VUS in *RYR2*: c.12944G > A (p.Gly4315Glu, rs766109950) and c.3256C > T (p.Arg1086Ter, rs371303783).

In patient 815c, who had a novel likely pathogenic variant c.556G > T (p.Val186Leu, rs201211033) in *RYR2*, provocation of ventricular arrhythmias during EEPS with isoproterenol failed.

If arrhythmic events and/or recorded episodes of sustained polymorphic and/or bidirectional VT were present despite the medical therapy carried out, an ICD was implanted for secondary prevention of SCD. ATP therapy (Ramp) and appropriate ICD shocks were observed in 2 (25%) patients: patient 642c and the mother of proband 13m. Figs. 5–7 show an episode of sustained VT; after its detection, ATP therapy was sequenced twice (Ramp), and sinus rhythm was successfully restored.

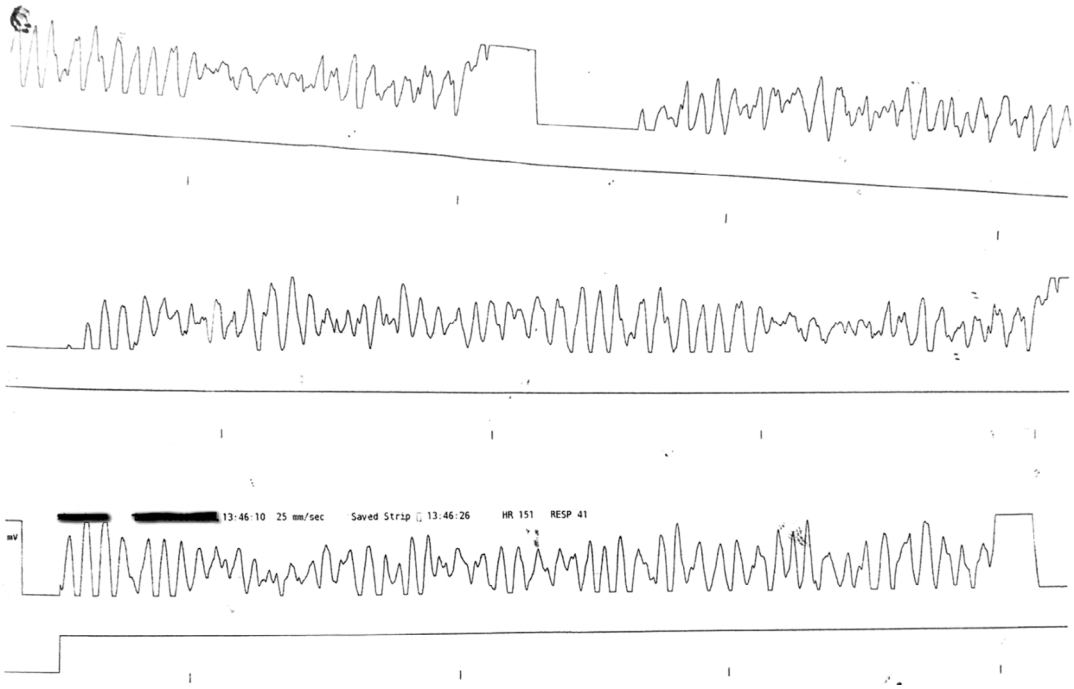

Fig. 4. ECG of patient 642c. ECG fragment with paroxysm of ventricular fibrillation
Рис. 4. ЭКГ пациента 642с. Фрагмент ЭКГ с пароксизмом крупноволновой ФЖ

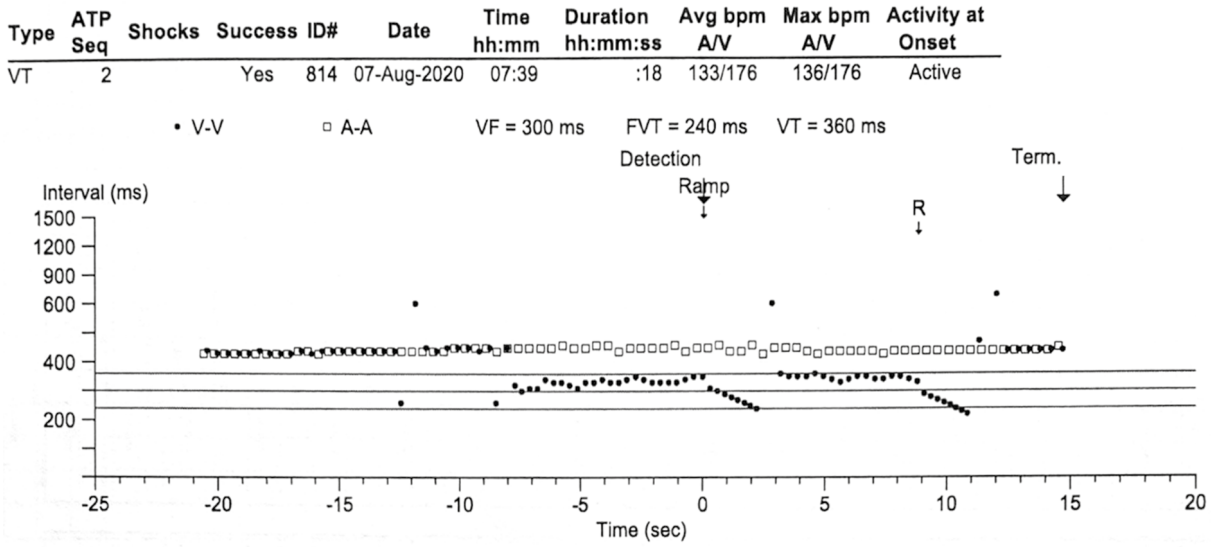

Fig. 5. The trend of ICD of proband's 13m mother representing episodes of sustained VT with ATP therapy
Рис. 5. Тренд ИКД матери пробанда 13м, представляющий эпизод устойчивой ЖТ с АТР-терапией

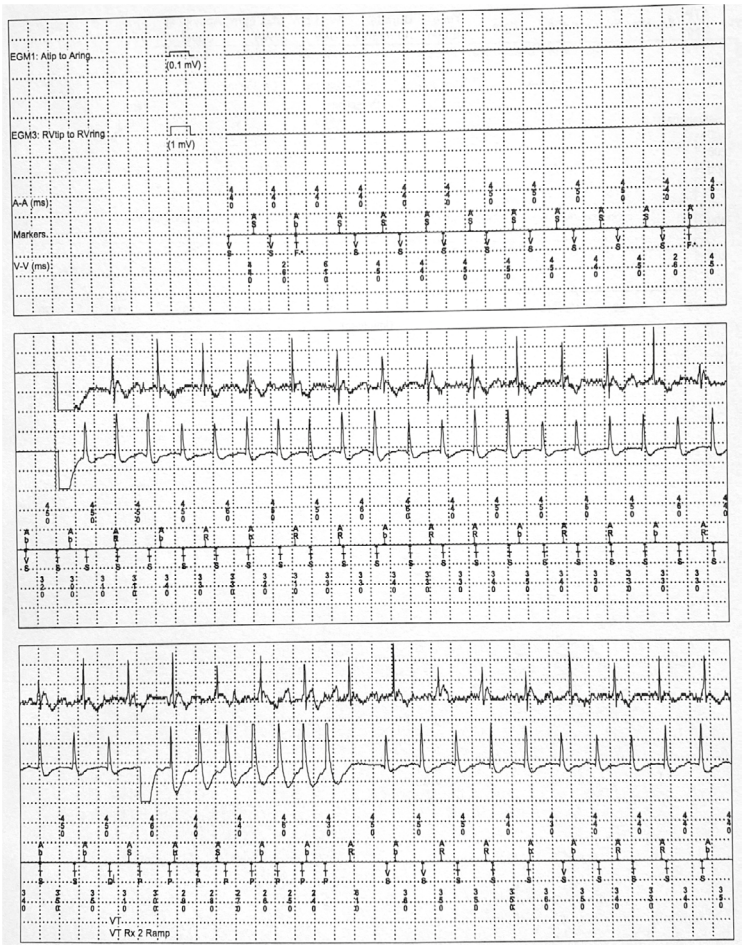

Fig. 6. Endogram fragment of proband's 13m mother representing the episode of sustained VT with the 1st attempt of Ramp ATP therapy (inefficient)
Рис. 6. Фрагмент эндограммы матери пробанда 13м, на которой представлен эпизод устойчивой ЖТ с 1-й попыткой АТР-терапии Ramp (безуспешной)

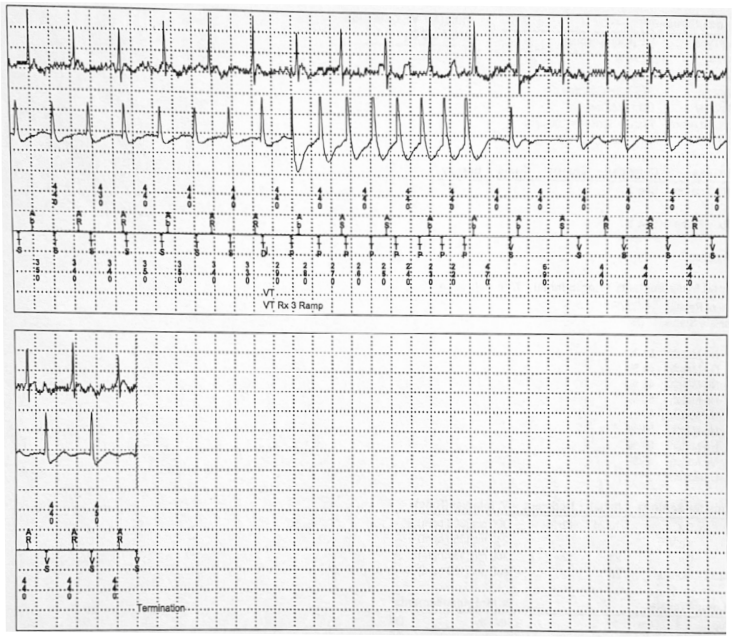

Fig. 7. Endogram fragment of proband's 13m mother representing the episode of sustained VT with the 2nd attempt of Ramp ATP therapy (efficient) and restoration of sinus rhythm
Рис. 7. Фрагмент эндограммы матери пробанда 13м, на которой представлен эпизод устойчивой ЖТ с 2-й попыткой АТР-терапии Ramp (успешной) и восстановлением синусового ритма

DISCUSSION

This study presented the clinical and genetic characteristics of eight patients with CPVT and *RYR2* mutations. The phenotypes of probands with CPVT shared common clinical manifestations: syncope episodes were usually triggered by physical activity or emotion, and in patient 642c, the disease manifested with cardiovascular arrest caused by VF at the age of 15 years. The median age of onset of CPVT symptoms in the observed probands (32 [28–41] years) is comparable to previously reported probands with *RYR2* mutations [18, 19]. However, some individuals with *RYR2* mutations may have a much later age of CPVT onset. In our study, 3 (37.5%) patients were asymptomatic until the age of 40 years. Various arrhythmias peculiar to CPVT were noted in the patients observed. To illustrate, the baseline resting ECG registered a transient prolonged *QTc* interval of up to 500 ms in 50% of the patients, and the majority had sinus bradycardia [20], as previously reported in non-genotyped populations [21, 22].

The fact that patients with CPVT and *RYR2* mutation exhibit significant bradycardia may help in the molecular diagnosis of (young) patients without structural heart diseases manifested by syncope events and slow heart rates but with normal *QTc* on resting ECG. For instance, a study of 29 non-genotyped Japanese patients of the same age with CPVT demonstrated sinus bradycardia [22]. This may be due to the presence of RYR2 channels in the functional SR of sinoatrial node cells, which serve as the main cardiac pacemakers [23]. Moreover, substances that impair SR function, such as ryanodine and cyclopiazonic acid, have negative chronotropic effects [23].

Thus, the bradycardia observed in carriers of *RYR2* mutations may be a direct implication of impaired Ca^{2+} regulation in sinoatrial node cells. However, this phenomenon may represent a vagus nerve feedback loop; a low mean heart rate reduces the likelihood of reaching the critical threshold of CPVT induction.

In this study, *QT* prolongation was observed in 50% of the patients with CPVT. Previous studies have demonstrated that certain CPVT cases were misdiagnosed as LQTS. Approximately 30% of patients with CPVT were misdiagnosed with LQTS in the presence of transient moderate *QT* prolongation of > 460 ms [9]. Tester et al. conveyed that nearly 6% of 269 patients with LQTS without mutations in genes associated with this pathology had *RYR2* mutations, which is primarily associated with CPVT [3]. Medeiros-Domingo et al. found that nearly one-third of patients with "atypical/probable" LQTS and exercise-induced syncope and *QT* with 480 ms had a missense *RYR2* mutation, indicating the need for differential diagnosis between LQTS and CPVT [10]. In a Japanese study by Ozawa et al [9], *RYR2* mutations were detected in 9 of 104 patients initially diagnosed with LQTS. They were misdiagnosed for four different reasons: (1) transient prolongation of the *QTc* after cardiopulmonary resuscitation, (2) prolongation of the *QTc* after epinephrine testing, (3) absence of ventricular arrhythmias on exercise testing, and (4) assumption of LQTS without evidence. CPVT-related ventricular arrhythmias can be reproduced during exercise testing or isoproterenol infusion. The induction of bidirectional VT establishes CPVT in the presence of a "borderline interval" of the *QTc*. Nevertheless, relatively few patients with *RYR2* mutations were reported to have an LQTS phenotype or an overlapping phenotype such as LQTS and CPVT [24].

The described clinical cases of patients with CPVT showed episodes of non-sustained polymorphic VT, unrelated to physical activity, against the background of bradycardia with episodes of transient *QTc* prolongation. In an 8-year-old proband, SCD resulted from polymorphic VT, which transformed into VF. The proband's mother (32 years old) had an ICD implanted for primary SCD prevention; hence, no exercise stress test could be performed. During follow-up, the *QTc* interval remained within the normal range; although, an appropriate ICD therapy for non-sustained polymorphic VT was recorded. Furthermore, in this study, CPVT episodes were not associated with physical activity and occurred at rest or under stress.

No international consensus diagnostic criteria exist to distinguish CPVT from LQTS, and definitive diagnosis is challenging in patients with both *QT* prolongation and polymorphic VT. Combined channelopathies with a phenotype of both CPVT and LQT may exist. For instance, Makita et al. [25] reported that two of five cases with mutations in the calmodulin gene showed overlapping signs of CPVT and LQTS. Further studies are needed to elucidate the causes of *QT* prolongation in patients with mutations in CPVT-associated genes.

Supraventricular arrhythmias such as AVNRT and AF, followed by ventricular arrhythmias, were recorded in 2 (25%) patients. Early active detection of supraventricular rhythm disorders in these patients is an additional tool of increasing the stress resistance of the ventricular myocardium and reducing the risk of ventricular arrhythmias.

Beta-blocker therapy in our patients had a generally favorable outcome, with seven of eight patients remaining asymptomatic at a mean follow-up of 6 years. Unfortunately, SCD occurred in one patient due to medical noncompliance following appropriate diagnosis and treatment. The doses of beta-blockers required to maintain the asymptomatic course of CPVT are higher than those used in LQTS [26].

ICDs were implanted in 4 (50%) patients who had polymorphic ventricular tachyarrhythmias during the stress testing (EEPS with epinephrine/isoproterenol) or 24-hour Holter monitoring.

The European Society of Cardiology Guidelines for the Management of Patients with Ventricular Arrhythmias and Prevention of Sudden Cardiac Death (ESC-2022) recommend ICD implantation in combination with beta-blockers and flecainide in patients with CPVT following an interrupted cardiac arrest (class I, level of evidence C). In addition, ICD implantation should be considered in patients with CPVT who have arrhythmogenic syncope and/or documented bidirectional/polymorphic VT while receiving the maximum tolerated dose of beta-blockers and flecainide (class IIa, level of evidence C) [27].

CONCLUSIONS

In summary, the clinical and genetic characteristics of patients with CPVT made it possible to evaluate clinical features, response to therapy, and genotype–phenotype correlation. Transient *QTc* prolongation, marked sinus bradycardia, and supraventricular tachyarrhythmias, followed by life-threatening ventricular tachyarrhythmias, are common in patients with CPVT and should be considered in the early diagnosis and selection of preventive strategies.

Limitations of the study

The study limitations include the relatively small number of patients due to the low incidence of the disease.

ADDITIONAL INFORMATION

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

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REFERENCES

1. Leenhardt A, Denjoy I, Guicheney P. Catecholaminergic polymorphic ventricular tachycardia. *Circ Arrhythm Electrophysiol*. 2012;5(5):1044–1052. DOI: 10.1161/CIRCEP.111.962027

2. Sumitomo N. Current topics in catecholaminergic polymorphic ventricular tachycardia. *J Arrhythmia*. 2016;32(5):344–351. DOI: 10.1016/j.joa.2015.09.008

3. Tester DJ, Kopplin LJ, Will ML, Ackerman MJ. Spectrum and prevalence of cardiac ryanodine receptor (RyR2) mutations in a cohort of unrelated patients referred explicitly for long QT syndrome genetic testing. *Heart Rhythm*. 2005;2(10):1099–10105. DOI: 10.1016/j.hrthm.2005.07.012

4. Marks AR. Ryanodine receptors/calcium release channels in heart failure and sudden cardiac death. *J Mol Cell Cardiol*. 2001;33(4):615–624. DOI: 10.1006/jmcc.2000

5. Priori SG, Napolitano C, Tiso N, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2001;103(2): 196–200. DOI: 10.1161/01.cir.103.2.196

6. Blayney LM, Lai FA. Ryanodine receptor-mediated arrhythmias and sudden cardiac death. *Pharmacol Ther*. 2009;123(2):151–177. DOI: 10.1016/j.pharmthera.2009.03.006

7. Lahat H, Pras E, Olender T, et al. A missense mutation in a highly conserved region of CASQ2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel. *Am J Hum Genet*. 2001;69(6): 1378–1384. DOI: 10.1086/324565

8. Postma AV, Denjoy I, Hoorntje TM, et al. Absence of calsequestrin 2 causes severe forms of catecholaminergic polymorphic ventricular tachycardia. *Circ Res*. 2002;91(8):e21–26. DOI: 10.1161/01.res.0000038886.18992.6b

9. Ozawa J, Ohno S, Fujii Y, et al. Differential diagnosis between catecholaminergic polymorphic ventricular tachycardia and long QT syndrome type 1 – modified Schwartz score. *Circ J*. 2018;82(9): 2269–2276. DOI: 10.1253/circj.CJ-17-1032

10. Medeiros-Domingo A, Bhuiyan ZA, Tester DJ, et al. The RYR2-encoded ryanodine receptor/calcium release channel in patients diagnosed previously with either catecholaminergic polymorphic ventricular tachycardia or genotype negative, exercise-induced long QT syndrome: a comprehensive open reading frame mutational analysis. *J Am Coll Cardiol*. 2009;5(22):2065–2074. DOI: 10.1016/j.jacc.2009.08.022

11. Glukhov AV, Kalyanasundaram A, Lou Q, et al. Calsequestrin 2 deletion causes sinoatrial node dysfunction and atrial arrhythmias

associated with altered sarcoplasmic reticulum calcium cycling and degenerative fibrosis within the mouse atrial pacemaker complex1. *Eur Heart J*. 2015;36(11):686–697. DOI: 10.1093/eurheartj/eht452

12. Faggioni M, Hwang HS, van der Werf C, et al. Accelerated sinus rhythm prevents catecholaminergic polymorphic ventricular tachycardia in mice and in patients. *Circ Res*. 2013;112(4):689–697. DOI: 10.1161/CIRCRESAHA.111.300076

13. Postma AV, Denjoy I, Kamblock J, et al. Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients. *J Med Genet*. 2005;42(11):863–870. DOI: 10.1136/jmg.2004.028993

14. van der Werf C, Nederend I, Hofman N, et al. Familial evaluation in catecholaminergic polymorphic ventricular tachycardia: disease penetrance and expression in cardiac ryanodine receptor mutation-carrying relatives. *Circ Arrhythm Electrophysiol*. 2012;5(4):748–756. DOI: 10.1161/CIRCEP.112.970517

15. Sumitomo N, Sakurada H, Taniguchi K, et al. Association of atrial arrhythmia and sinus node dysfunction in patients with catecholaminergic polymorphic ventricular tachycardia. *Circ J*. 2007;71(10):1606–1609. DOI: 10.1253/circj.71.1606

16. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1–39.e14. DOI: 10.1016/j.echo.2014.10.003

17. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405–424. DOI: 10.1038/gim.2015.30

18. Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation*. 2002;106(1):69–74. DOI: 10.1161/01.cir.0000020013.73106.d8

19. Choi G, Kopplin LJ, Tester DJ, et al. Spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmia syndromes. *Circulation*. 2004;11(15):2119–2124. DOI: 10.1161/01.CIR.0000144471.98080.CA

20. Rijnbeek PR, Witsenburg M, Schrama E, et al. New normal limits for the paediatric electrocardiogram. *Eur Heart J*. 2001;22(8):702–711. DOI: 10.1053/euhj.2000.2399

21. Leenhardt A, Lucet V, Denjoy I, et al. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. *Circulation*. 1995;91(5):1512–1519. DOI: 10.1161/01.cir.91.5.1512

22. Sumitomo N, Harada K, Nagashima M, et al. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death. *Heart*. 2003;89(1):66–70. DOI: 10.1136/heart.89.1.66

23. Rigg L, Heath BM, Cui Y, Terrar DA. Localisation and functional significance of ryanodine receptors during beta-adrenoceptor stimulation in the guinea-pig sino-atrial node. *Cardiovasc Res*. 2000;48(2):254–264. DOI: 10.1016/s0008-6363(00)00153-x

24. Shigemizu D, Aiba T, Nakagawa H, et al. Exome analyses of long QT syndrome reveal candidate pathogenic mutations in calmodulin-interacting genes. *PLoS One*. 2015;10(7):e0130329. DOI: 10.1371/journal.pone.0130329

25. Makita N, Yagihara N, Crotti L, et al. Novel calmodulin mutations associated with congenital arrhythmia susceptibility. *Circ Cardiovasc Genet*. 2014;7(4):466–474. DOI: 10.1161/CIRCGENETICS.113.000459

26. Ackerman MJ, Priori SG, Dubin AM, et al. Beta-blocker therapy for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia: Are all beta-blockers equivalent? *Heart Rhythm*. 2017;14(1):e41–e44. DOI: 10.1016/j.hrthm.2016.09.012

27. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;43(40):3997–4126. DOI: 10.1093/eurheartj/ehac262

СПИСОК ЛИТЕРАТУРЫ

1. Leenhardt A., Denjoy I., Guicheney P. Catecholaminergic polymorphic ventricular tachycardia // Circ Arrhythm Electrophysiol. 2012. Vol. 5, No. 5. P. 1044–1052. DOI: 10.1161/CIRCEP.111.962027

2. Sumitomo N. Current topics in catecholaminergic polymorphic ventricular tachycardia // J Arrhythmia. 2016. Vol. 32, No. 5. P. 344–351. DOI: 10.1016/j.joa.2015.09.008

3. Tester D.J., Kopplin L.J., Will M.L., Ackerman M.J. Spectrum and prevalence of cardiac ryanodine receptor (RyR2) mutations in a cohort of unrelated patients referred explicitly for long QT syndrome genetic testing // Heart Rhythm. 2005. Vol. 2, No. 10. P. 1099–10105. DOI: 10.1016/j.hrthm.2005.07.012

4. Marks A.R. Ryanodine receptors/calcium release channels in heart failure and sudden cardiac death // J Mol Cell Cardiol. 2001. Vol. 33, No. 4. P. 615–624. DOI: 10.1006/jmcc.2000

5. Priori S.G., Napolitano C., Tiso N., et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia // Circulation. 2001. Vol. 103, No. 2. P. 196–200. DOI: 10.1161/01.cir.103.2.196

6. Blayney L.M., Lai F.A. Ryanodine receptor-mediated arrhythmias and sudden cardiac death // Pharmacol Ther. 2009. Vol. 123, No. 2. P. 151–177. DOI: 10.1016/j.pharmthera.2009.03.006

7. Lahat H., Pras E., Olender T., et al. A missense mutation in a highly conserved region of CASQ2 is associated with autosomal recessive catecholamine-induced polymorphic ventricular tachycardia in Bedouin families from Israel // Am J Hum Genet. 2001. Vol. 69, No. 6. P. 1378–1384. DOI: 10.1086/324565

8. Postma A.V., Denjoy I., Hoorntje T.M., et al. Absence of calsequestrin 2 causes severe forms of catecholaminergic polymorphic ventricular tachycardia // Circ Res. 2002. Vol. 91, No. 8. P. e21–26. DOI: 10.1161/01.res.0000038886.18992.6b

9. Ozawa J., Ohno S., Fujii Y., et al. Differential diagnosis between catecholaminergic polymorphic ventricular tachycardia and long QT syndrome type 1 – modified Schwartz score // Circ J. 2018. Vol. 82, No. 9. P. 2269–2276. DOI: 10.1253/circj.CJ-17-1032

10. Medeiros-Domingo A., Bhuiyan Z.A., Tester D.J., et al. The RYR2-encoded ryanodine receptor/calcium release channel in patients diagnosed previously with either catecholaminergic polymorphic ventricular tachycardia or genotype negative, exercise-induced long QT syndrome: a comprehensive open reading frame mutational analysis // J Am Coll Cardiol. 2009. Vol. 5, No. 22. P. 2065–2074. DOI: 10.1016/j.jacc.2009.08.022

11. Glukhov A.V., Kalyanasundaram A., Lou Q., et al. Calsequestrin 2 deletion causes sinoatrial node dysfunction and atrial arrhythmias associated with altered sarcoplasmic reticulum calcium cycling and degenerative fibrosis within the mouse atrial pacemaker complex1 // Eur Heart J. 2015. Vol. 36, No. 11. P. 686–697. DOI: 10.1093/eurheartj/eht452

12. Faggioni M., Hwang H.S., van der Werf C., et al. Accelerated sinus rhythm prevents catecholaminergic polymorphic ventricular tachycardia in mice and in patients // Circ Res. 2013. Vol. 112, No. 4. P. 689–697. DOI: 10.1161/CIRCRESAHA.111.300076

13. Postma A.V., Denjoy I., Kamblock J., et al. Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients // J Med Genet. 2005. Vol. 42, No. 11. P. 863–870. DOI: 10.1136/jmg.2004.028993

14. van der Werf C., Nederend I., Hofman N., et al. Familial evaluation in catecholaminergic polymorphic ventricular tachycardia: disease penetrance and expression in cardiac ryanodine receptor mutation-carrying relatives // Circ Arrhythm Electrophysiol. 2012. Vol. 5, No. 4. P. 748–756. DOI: 10.1161/CIRCEP.112.970517

15. Sumitomo N., Sakurada H., Taniguchi K., et al. Association of atrial arrhythmia and sinus node dysfunction in patients with catecholaminergic polymorphic ventricular tachycardia // Circ J. 2007. Vol. 71, No. 10. P. 1606–1609. DOI: 10.1253/circj.71.1606

16. Lang R.M., Badano L.P., Mor-Avi V., et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging // J Am Soc Echocardiogr. 2015. Vol. 28, No. 1. P. 1–39.e14. DOI: 10.1016/j.echo.2014.10.003

17. Richards S., Aziz N., Bale S., et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology // Genet Med. 2015. Vol. 17, No. 5. P. 405–424. DOI: 10.1038/gim.2015.30

18. Priori S.G., Napolitano C., Memmi M., et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia // Circulation. 2002. Vol. 106, No. 1. P. 69–74. DOI: 10.1161/01.cir.0000020013.73106.d8

19. Choi G., Kopplin L.J., Tester D.J., et al. Spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmia syndromes // Circulation. 2004. Vol. 11, No. 15. P. 2119–2124. DOI: 10.1161/01.CIR.0000144471.98080.CA

20. Rijnbeek P.R., Witsenburg M., Schrama E., et al. New normal limits for the paediatric electrocardiogram // Eur Heart J. 2001. Vol. 22, No. 8. P. 702–711. DOI: 10.1053/euhj.2000.2399

21. Leenhardt A., Lucet V., Denjoy I., et al. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients // Circulation. 1995. Vol. 91, No. 5. P. 1512–1519. DOI: 10.1161/01.cir.91.5.1512

22. Sumitomo N., Harada K., Nagashima M., et al. Catecholaminergic polymorphic ventricular tachycardia: electrocardiographic characteristics and optimal therapeutic strategies to prevent sudden death // Heart. 2003. Vol. 89, No. 1. P. 66–70. DOI: 10.1136/heart.89.1.66

23. Rigg L., Heath B.M., Cui Y., Terrar D.A. Localisation and functional significance of ryanodine receptors during beta-adrenoceptor stimulation in the guinea-pig sino-atrial node // Cardiovasc Res. 2000. Vol. 48, No. 2. P. 254–264. DOI: 10.1016/s0008-6363(00)00153-x

24. Shigemizu D., Aiba T., Nakagawa H., et al. Exome analyses of long QT syndrome reveal candidate pathogenic mutations in calmodulin-interacting genes // PLoS One. 2015. Vol. 10, No. 7. ID e0130329. DOI: 10.1371/journal.pone.0130329

25. Makita N., Yagihara N., Crotti L., et al. Novel calmodulin mutations associated with congenital arrhythmia susceptibility // Circ Cardiovasc Genet. 2014. Vol. 7. No. 4. P. 466–474. DOI: 10.1161/CIRCGENETICS.113.000459

26. Ackerman M.J., Priori S.G., Dubin A.M., et al. Beta-blocker therapy for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia: Are all beta-blockers equivalent? // Heart Rhythm. 2017. Vol. 14, No. 1. P. e41–e44. DOI: 10.1016/j.hrthm.2016.09.012

27. Zeppenfeld K., Tfelt-Hansen J., de Riva M., et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death // Eur Heart J. 2022. Vol. 43, No. 40. P. 3997–4126. DOI: 10.1093/eurheartj/ehac262

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