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FAMILIAL *RBM20*-CARDIOMYOPATHY: VARIOUS CLINICAL PHENOTYPES. CASE REPORT

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Genetic causes are increasingly found to be responsible for the development of sudden death in young people. Since 2009, pathogenic mutations in RBM20 gene were recognized as an important cause of dilated cardiomyopathy (DCM) and sudden cardiac death (SCD). The high risk of malignant ventricular arrhythmias in RBM20-cardiomyopathy has made these patients potential candidates for the implantable cardioverter-defibrillator for primary prevention of SCD. The presented clinical case of malignant pathogenic mutation in the RBM20 gene demonstrates different phenotypes, including DCM, SCD and asymptomatic forms in one family. Moreover, for the first time we described the presence of prolonged QT interval due to the fusion with U wave on ECG in carries of this malignant familial mutation. The prolonged QT interval may contribute to the development of ventricular arrhythmias and the increased risk of SCD in patients with this rare genetic pathology.

Key words: *RMB20*-cardiomyopathy; syncope; sudden cardiac death; ventricular arrhythmias; dilated cardiomyopathy; implantable cardioverter-defibrillator
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Sudden cardiac death (SCD) accounts for more than 4 million cases worldwide each year [1]. Although the risk of SCD increases with age, cases of sudden death among young adults are not uncommon. Today, according to official statistics, between 1100-9000 young people die suddenly each year in Europe and between 800-6200 in the USA [2, 3]. In those cases when no structural heart disease can be detected by autopsy, the cause of sudden death is malignant ventricular arrhythmias due to genetically determined channelopathies (Brugada syndrome, prolonged QT syndrome, catecholamine-dependent ventricular tachycardia) [4]. At the same time, malignant ventricular arrhythmias may serve as only one manifestation of severe structural heart disease, one of which is dilated cardiomyopathy (DCMP).

The genetic causes of DCMP are extremely heterogeneous. More than 100 genes with different functions have

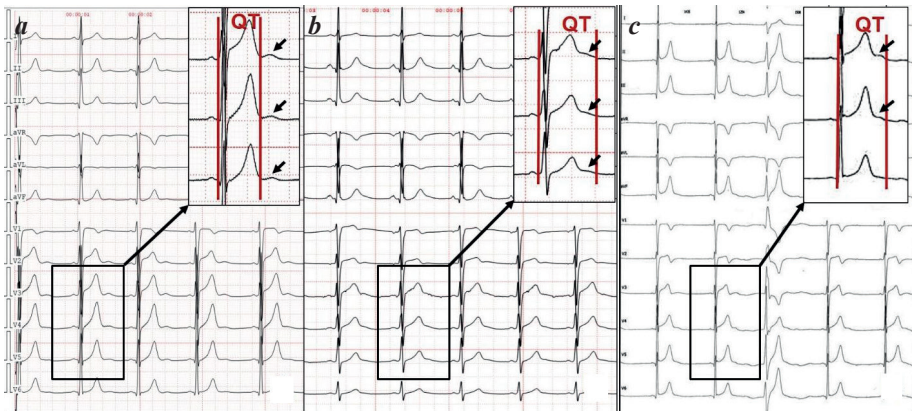

Fig. 1. Electrocardiography (ECG) of patient A.: a - resting ECG, heart rate (HR) 61 beats/min, QT = 400 ms, QTc = 472 ms. (note the presence of discrete U-wave mainly in the lateral thoracic leads - marked by arrows; b - repeatedly taken resting ECG, HR = 76 bpm, QT = 440 ms, QTc = 512 ms (U-wave is superimposed on the end part of the T wave); c - fragment of Holter ECG recording (at minimum HR 52 beats/min, QT = 520 ms, U-wave becomes part of the T wave (marked with arrows), QT interval is marked with vertical lines. QT interval value was determined according to E.Lepeshkin and B.Surawicz, 1953 [10]. The recording speed is 25 mm/s.

been described to be associated with the development of DCMP [5], and the list of genes of interest continues to grow. These include genes encoding sarcomeric proteins responsible for cytoarchitectonics and integrity of the nuclear membrane, carrying out ion transport and ensuring mitochondrial function [6]. The DCMP Working Group of the international Clinical Genome Consortium (https://clinicalgenome.org/) has conducted a detailed analysis of the evidence base of the continuously growing body of data on the association of genetic alterations with the development of monogenic DCMP. Of the entire spectrum of genes, only 19 (*ACTC1, ACTN2, BAG3, DES, DSP, FLNC, JPH2, LMNA, MYH7, NEXN, PLN, RBM20, SCN5A, TNNC1, TNNT2, TNNI3, TPM1, TTN, VCL*) have a sufficient clinical, pathophysiologic, and experimental evidence base, and it is these genes that are currently recommended for routine genetic diagnosis of DCMP [7].

Mutations in the *RBM20* gene (RNA binding motif protein, 20), which controls cardiac-specific splicing of several genes encoding ion channels and sarcomeric proteins, are responsible for 2-3% of familial DCMP cases [8]. The clinical manifestations of *RBM20*-associated forms of DCMP are characterized by a high risk of malignant ventricular cardiac rhythm disturbances, making these patients potential candidates for implantation of devices for primary prevention of SCD [9]. In the present study, we describe a familial form of DCMP with life-threatening rhythm disturbances caused by a heterozygous mutation NM_001134363:c.1907G>A (p.Arg636His) in the *RBM20* gene.

Patient A (III.1) was hospitalized for evaluation following a single episode of loss of consciousness, which occurred during physical and emotional exertion. Loss of consciousness was accompanied by muscle «twitches». After 1 to 2 minutes, the patient regained consciousness. An ambulance crew was called and recorded sinus tachycardia with a heart rate of up to 125 beats per minute on the electrocardiogram (ECG).

No pathology was detected during inpatient physical examination. According to the results of the laboratory examination, all indices were within normal values for general and biochemical blood tests, as well as thyroid hormone levels. The specific values were as follows: potassium – 5.1 mmol/L, magnesium – 1.05 mmol/L, pro-BNP – 69.5 pg/mL*, free T4 – 16.41 pmol/L, and thyroid-stimulating hormone (TSH) – 1.45* mIU/mL*. The results of echocardiography (Echo) confirmed normal values of left ventricular (LV) end-diastolic dimension (EDD) and end-diastolic volume (EDV) (LV EDD = 5.6 cm with normal values up to 5.8 cm in men, LV EDV = 146 ml with normal values up to 150 ml in men). It revealed a slight increase in LV end-systolic dimension (ESD) (4.4 cm, with a norm of up to 4.0 cm in men) and indexed LV EDV (78.1 ml/m², with a norm of up to 74 ml/m² in men), an increase in LV end-systolic volume (ESV) (76 ml, with a norm of up to 61 ml in men), as well as indexed LV ESR (40.6 ml/m², with a norm of up to 31 ml/m² - men). Moderately reduced left ventricular ejection fraction (LVEF) was 46-48%. The di-*

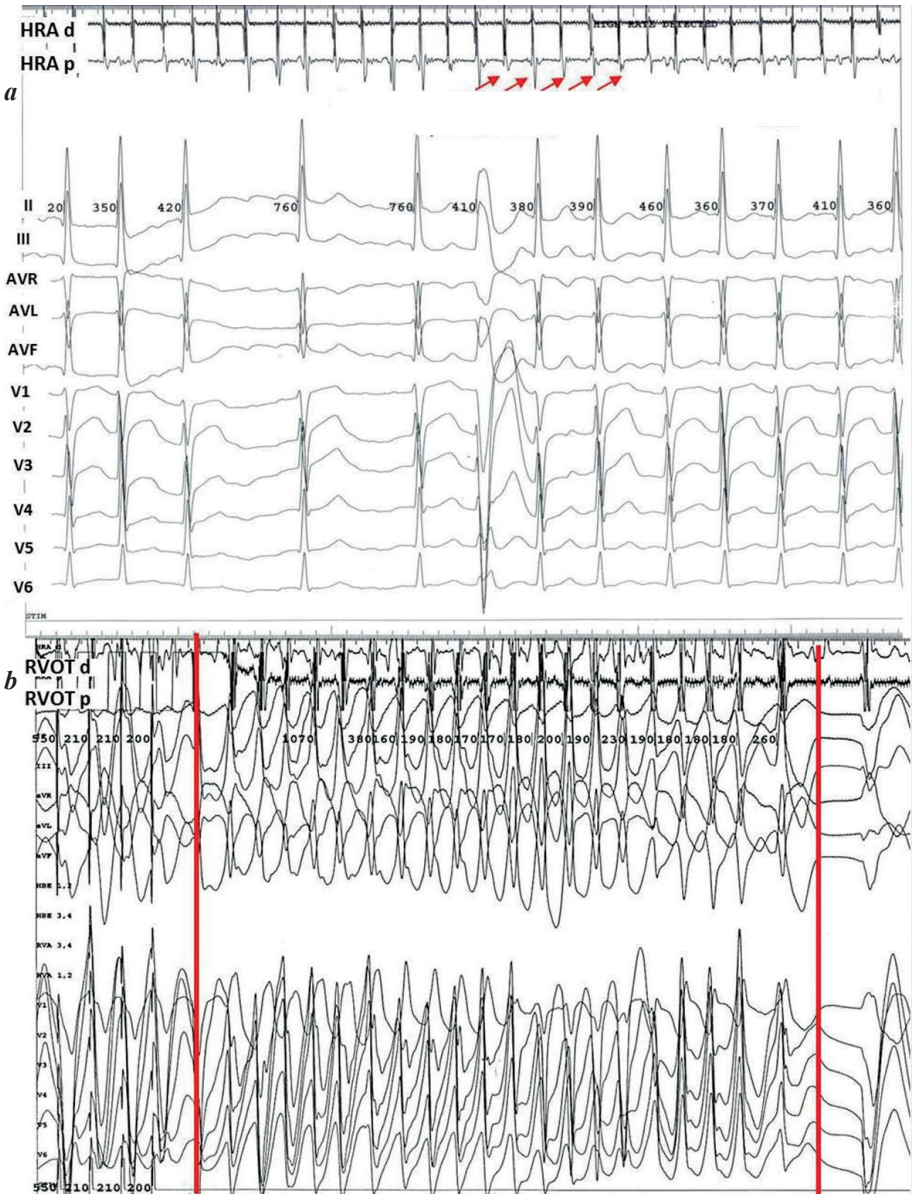

Fig. 2. Results of electrophysiological study of the heart of patient A.: a - induction of paroxysm of atypical atrial flutter with transition to atrial fibrillation with HR=150-190 beats per minute during program stimulation by a single extrastimulus; b - induction of an episode of polymorphic ventricular tachycardia with duration of 4 s during program stimulation of the right ventricle by a triple extrastimulus.

mensions of the right heart chambers and left atrium left and right ventricular wall thickness were within normal limits. No pathology of the valve apparatus was detected, mitral and tricuspid regurgitation corresponded to the first degree.

Due to deviations from normal values in several echocardiographic (Echo) parameters, and in accordance with the new 2022 recommendations from the European Society of Cardiology on the diagnosis and treatment of ventricular arrhythmias [9], the patient underwent cardiac magnetic resonance imaging (MRI) with intravenous gadolinium contrast. The results of this study also confirmed LV cavity enlargement (LV EDD 6.0 cm, LV ESD 5.2 cm, LV EDV 185.8 ml, LV EDV indexed 99.2 mL/m^2), as well as a slightly more pronounced decrease in LVEF (40%). No signs of the phenomenon of «late accumulation» of contrast agent in the ventricular myocardium were detected.

The episode of syncope in Patient A prompted a more detailed examination due to a significantly aggravated family history, which included three cases of sudden cardiac death at a young age. Two of these cases were associated with physical and emotional exertion, while one occurred at rest, during sleep at night. This required exclusion of a wide range of inherited heart diseases, most notably prolonged QT and Brugada syndromes and catecholamine-dependent ventricular tachycardia.

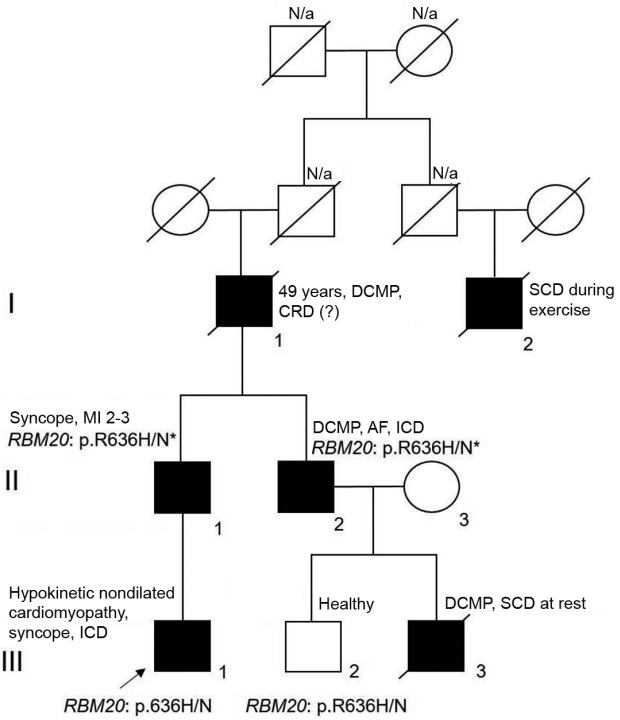

Fig. 3. Pedigree of patient A's family, where proband is shown by arrow, closed symbols show family members with indications of DCMP and/or who died suddenly, crossed-out symbols show deceased family members, age at death is indicated if known. Generation numbers are indicated by Roman numerals, the number of a person in a generation by Arabic numerals. RBM20: p.636H/N is a carrier of the p.R636H mutation in the RBM20 gene in a heterozygous state, genetically confirmed. RBM20: p.6436H/N* is an obligate carrier of the p.R636H mutation in the RBM20 gene, genetically unconfirmed. SCD - sudden cardiac death, DCMP - dilated cardiomyopathy, ICD - implantable cardioverter-defibrillator, MI - mitral insufficiency, CRD - cardiac rhythm disturbances, AF - atrial fibrillation, CHF - chronic heart failure.

When analyzing the resting ECG of the proband (Fig. 1), no Brugada ECG phenomenon was detected. However, the presence of a discrete U wave was noted, which in some leads was superimposed on the descending knee of the T wave. At normal values of the QT interval there was an increase in the corrected value of this index up to 470-500 ms (Fig. 1a,b). QT interval prolongation was also registered according to Holter ECG monitoring data: against the background of minimal heart rate (HR) of 52 beats per minute the absolute value of QT interval amounted to 520 ms (Fig. 1c), while no significant rhythm disturbances were registered in the patient.

To exclude Brugada syndrome, we performed a provocative diagnostic test with a class IA drug (procainamide, 10 mg/kg for 20 min) [11]. The test did not reveal any changes in the morphology of the QRS complex or the ST segment in leads V1 and V2, which are characteristic of Brugada syndrome. This allowed for the exclusion of Brugada syndrome as a diagnosis.

To exclude catecholamine-dependent ventricular tachycardia, we performed an epinephrine test according to the Mayo Clinic protocol [12]. During the assay with a maximum dose of 0.3 μg/kg/min, the appearance of ventricular extrasystoles was noted. However, the polymorphic ventricular tachycardia, which is pathognomonic for this congenital channelopathy, was not induced.

Although the use of the epinephrine test to exclude long QT syndrome does not appear in the 2022 clinical recommendations for the diagnosis and treatment of ventricular tachycardia [9], as it did in previous versions, we observed an increase in the QT interval (from 420 to 480 ms) and the corrected QT interval (from 383 to 529 ms) during the administration of epinephrine at a dose of 0.05-0.1 μg/kg/min. This increase was disproportionate to the rise in heart rate (from 49 to 73 beats per minute).

Given the association of syncope with physical activity, a physical load test on a bicycle ergometer with abrupt cessation of the load was performed. No heart rhythm disturbances were induced during the test, no decrease in blood pressure was recorded. There was a prolongation of the QTc interval up to 520 ms in the early recovery period. Prolongation of the corrected QT interval to 530 ms was again also noted during stress-echo at the height of exercise. However, no signs of occult coronary artery disease were detected. Rare single supraventricular and ventricular extrasystoles were recorded during the test. According to current recommendations, an increase in the corrected QT interval value during the early recovery period may support the diagnosis of long QT syndrome [13]. However, the Echo and cardiac MRI data, which indicated a decrease in left ventricular (LV) systolic function and LV cavity dilation, did not align with the typical presentation of primary «electrical heart disease.» According to the 2022 consensus document from the working group on myocardial and pericardial diseases

of the European Society of Cardiology, the presence of global LV systolic dysfunction, defined as a ejection fraction (EF) < 45%, not attributable to abnormal filling or coronary artery disease and confirmed by echocardiography and MRI, is consistent with the diagnosis of hypokinetic cardiomyopathy [14]. In the European Society of Cardiology's 2023 clinical guidelines on cardiomyopathies, the term «hypokinetic nondilated cardiomyopathy» has been replaced by «left ventricular nondilated cardiomyopathy.» This updated term encompasses all cases of non-ischemic LV pathology, including those with scarring or fatty infiltration, regardless of whether there is local or global contractility impairment, as well as cases of LV hypokinesia without scarring [15].

Given that the cause of syncope remained unknown, an intracardiac electrophysiologic study (EPS) was conducted on the patient with LV nondilated cardiomyopathy, in accordance with both European and national guidelines [9]. According to the electrophysiologic study results, atrioventricular conduction and conduction through the His-Purkinje system were within normal limits. The AH interval was 72 ms (normal range: 55-125 ms), the HV interval was 52 ms (normal range: 35-55 ms), and the Wenckebach point of the AV node was also within normal limits, measured at 180 impulses per minute. Programmed stimulation with a single extrastimulus induced a paroxysm of atypical atrial flutter with transition to atrial fibrillation with CSF=150-190 beats/min (Fig. 2 a). This arrhythmia was of a persistent nature and required electrical pulse therapy.

Next, the patient underwent a standard protocol of frequent and programmed ventricular stimulation from two points - the right ventricular apex and the right ventricular outflow tract - using single, paired and triple extrastimuli until the effective ventricular refractory period was determined. Programmed stimulation of the right ventricle with triple extrastimulus induced 2 episodes of polymorphic ventricular tachycardia (VT) lasting 4 sec and 3.5 sec, which was accompanied by a sensation of dizziness (Fig. 2b). Reproducible induction of 2 erratic episodes of VT during programmed stimulation suggests the presence of an arrhythmogenic substrate for the development of clinically significant ventricular arrhythmias. Thus, during programmed cardiac stimulation during EPS, a spectrum of supraventricular and ventricular cardiac rhythm disturbances was detected, indicating «vulnerability» of both ventricular and atrial myocardium.

Analysis of the generally accepted diagnostic criteria of the prolonged QT syndrome with calculation of the corresponding scores [6, 14] reveals the presence of three features in our patient: 1) prolongation of the QTc interval more than 480 ms on the resting ECG (3 points on the scale); 2) syncope occurring on the background of stress (2 points); 3) unexplained sudden cardiac death among family members under 30 years of age (0.5 points). According to the algorithm for the diagnosis of prolonged QT syndrome [16], the patient was assigned a score of 5.5, which corresponds to «definite» prolonged QT syndrome. Thus, the clinical diagnosis at this stage was formulated as «Hypokinetic nondilated cardiomyopathy (familial). Heart rhythm disorder: prolonged QT syndrome. Syncope dated 9/25/2021.» Given the familial nature of the disease, the patient was referred for genetic counselling and DNA diagnosis [9]. The patient underwent whole exome sequencing (WES) searching for mutations in genes responsible for known primary arrhythmogenic syndromes and cardiomyopathies. The study in the patient revealed a rare genetic variant NM_001134363:c.1907G>A (p.R636H) in the RBM20 gene, in heterozygous state (Pathogenicity Class V, Pathogenic), repeatedly described in patients with DCMP [17-20].

Table 1.

Patient A's family pedigree

Member	Presence of RBM20 p.R636H/N mutation	Age 2022	LVEF (%)	Syncope	MI	CRD	QTc max	ICD
I.1	(?), untested	Died at age 49 (CHF).	n/a	n/a	n/a	n/a	n/a	-
I.2	(?), untested	Died at the age of 29 (SCD)	n/a	n/a	n/a	+	n/a	-
II.1	Bond carrier R636H, not tested	60	50-54%	+	2-3 degree	no	470	-
II.2	Bond carrier R636H, not tested	63	20-25%	no	2	AF	n/a	+
III.1	Proband, carrier R636H, confirmed	23	40%	+	3 degree	VCRD	530	+
III.2	Carrier R636H, confirmed	32	55-56%	no	0-1 degree	no	520	no
III.3	(?), untested	Died at the age of 29 (SCD)	DCMP	no	1-2	VCRD	500	-

Notes: SCD - sudden cardiac death, DCMP - dilated cardiomyopathy, VCRD - ventricular cardiac rhythm disturbances, ICD - implantable cardioverter-defibrillator, MI - mitral insufficiency, N/A - no data, CRD - cardiac rhythm disturbances, LVEF - left ventricular ejection fraction, AF - atrial fibrillation.

Thus, the patient evaluation plan we implemented in 2021 was in full compliance with the later version of the European clinical guidelines for the diagnosis and treatment of ventricular arrhythmias, released in 2022 [9]. According to these guidelines, it is recommended that implantation of a cardioverter-defibrillator (ICD) be considered in patients with hypokinetic nondilated cardiomyopathy when LVEF <50% and two risk factors (unexplained syncope and the presence of a pathogenic variant in the RBM20 gene) are present. Considering the patient's young age and the absence of indications for cardiac pacing*, a decision was made to implant a subcutaneous cardioverter-defibrillator. The surgery proceeded without any complications. The diagnosis was formulated as «Hypokinetic nondilated cardiomyopathy due to a mutation in the RBM20 gene.» Prolonged QT syndrome. Syncopal state. Implantation of subcutaneous cardioverter-defibrillator «EMBLEM MRI S-ICD». The patient was discharged with recommendations to check the parameters of the implanted subcutaneous ICD once every six months, to take metoprolol 50 mg/day under HR control, perindopril 4 mg/day under BP control, and to perform screening for carriage of the identified mutation in the RBM20 gene in available family members. During the dynamic follow-up of the patient during the next year, there were no arrhythmic events according to the data of telemetric monitoring of the subcutaneous ICD operation parameters. According to Echo data, no significant negative dynamics of heart chamber dimensions or myocardial contractile function was revealed.*

Considering the results of the genetic study, the family data were reanalyzed (Fig. 3). The medical history of a cousin (III.3) who died suddenly at the age of 29 years was reconstructed in detail (see Fig. 3, Table 1).

Progressive LV dysfunction was seen on a series of cardiac ultrasound findings of patient III.3 from the age of 18 years. Echo performed at the age of 23 years showed marked dilatation of the LV cavity (EDD 6.8 cm, ESD 5.9 cm), LVEF was 33%. The inflammatory genesis of DCMP was discussed, and the patient underwent cardiac MRI, which showed no evidence of contrast agent accumulation. Signs of active inflammatory myocardial damage were not detected and according to the results of endomyocardial biopsy, the pathomorphologic picture corresponded to dilated cardiomyopathy. An ICD for patient III.3 was not recommended at that time. When comparing the ECG of proband (Fig. 4a) and III.3 (Fig. 4b), both showed a U wave in the lateral thoracic leads. We carefully examined another relative (III.2) (see Fig. 3, Table 1), who at the time of examination (age 23 years) was practically healthy (according to Echo data, no enlargement of heart chambers was detected, LV EF 55-56%). The ECG of patient III.2 also showed a U wave in the lateral thoracic leads at a QT interval duration of 520 ms (Fig. 4c). Based on the results of cascade family screening, patient III.2 also had a p.R636H mutation in the RBM20 gene in a heterozygous state. Thus, family member III.2 is currently a genotype-positive phenotype-negative carrier of the pathogenic mutation. In accordance with the ESC 2023 guidelines [15], the patient was recommended to undergo contrast-enhanced cardiac MRI and dynamic follow-up.

According to family history, in two previous generations, three other family members (I.1, I.2, and II.2) were diagnosed with cardiac diseases. Patient II.2 has been observed for more than 10 years for DCMP, chronic heart failure with reduced LVEF (25%), paroxysmal atrial fibrillation, for which cryo-isolation of pulmonary vein orifices was performed. At the age of 53 years, he was fitted with an ICD for primary prevention of SCD, and no device activations were noted during the 10-year follow-up. The proband's father, patient II.1, was examined by us at the age of 60 years. According to the results of the examination, no dilatation of heart chambers, reduction of LV contractility were obtained, but myxomatous degeneration of mitral valve with mitral insufficiency of 2-3 degree was detected. Patient II.1 has a history of three syncopal episodes, two of which can be regarded as vasovagal syncope, and the third occurred during exercise. Patient II.1 refrained from further evaluation.

Thus, the autosomal dominant type of inheritance of malignant mutation manifested by DCMP, various heart rhythm disorders and SCD is traced in the family (Fig. 3, Table 1).

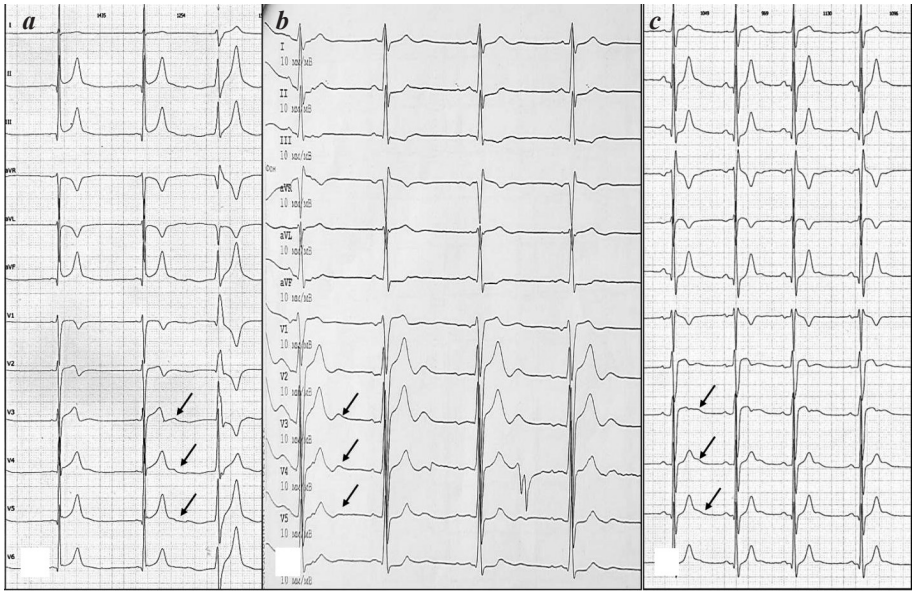

Fig. 4. ECGs of the patients of the family: a - ECG, proband, patient A (III.1), b - ECG, proband's suddenly deceased cousin (III.3) (discrete U wave seen), c - ECG of proband's second cousin (III.2), U wave seen as part of the QT interval (QT = 520 ms).

DISCUSSION

In 2009, the *RBM20* gene was added to the list of genes responsible for the development of cardiomyopathies with the risk of SCD. The malignancy of mutations in this gene was clearly demonstrated on the example of two families where cases of DCMP and SCD were registered for sever-

al generations [15]. The *RBM20* gene encodes a protein containing a motive for RNA recognition. This highly specialized protein is expressed in transverse striated muscle, the heart, and regulates the transcription and cardiac-specific translation of more than 30 proteins. The most studied target of *RBM20* splicing is the T*TN* gene, which encodes the giant sarcomeric protein titin. Importantly, mutations in the titin gene itself are frequent causes of DCMP, responsible for approximately 20% of familial cases and about 15% of sporadic cases of DCMP. Moreover, the course of *TTN*-mediated cardiomyopathies is characterized by less malignancy, which is explained by the diversity of intracellular targets of *RBM20* protein [21, 22].

In addition to titin, the *RBM20* gene regulates cardiac-specific splicing of ion channel genes (*CACNA1C, RYR2, TRDN*, et al.*)*, sarcomeric and sarcomeric-associated proteins (*ENAH, FHOD3, LDB3, LMO7, MLIP, MYH7, MYOMI, OBSCN, TNNT2*), calcium-calmodulin dependent kinases (*CAMK2G, CAMK2D, KALRN*, etc.*)*, and adhesive proteins responsible for intercellular interactions [22]. Notably, mutations in each of these target genes have been described as an independent cause of all known types of cardiomyopathies or arrhythmogenic syndromes (catecholamine-dependent ventricular tachycardia, prolonged QT syndrome, idiopathic VT). Therefore, disturbances in the amount or properties of RBM20 protein may be accompanied by a wide range of clinical manifestations, depending on which target proteins' functions may be impaired.

The present clinical observation is the first to demonstrate QT interval prolongation due to a U wave merging with the terminal part of the T wave in patients with familial cardiomyopathy caused by a mutation in the *RBM20* gene. To date, there is experimental scientific evidence of QT interval prolongation in laboratory animals with *RBM20* gene inactivated using gene knockout technique [23]. At the same time, there are no data on QT interval changes on ECG in the clinical cases of such familial cardiomyopathies available in the literature. The QT interval changes we found in members of the described family may be because of *RBM20* on calcium channel genes and may further contribute to arrhythmogenesis in this category of patients. Based on the results of the genetic study performed, a heterozygous substitution in exon 9 of the *RBM20* gene, c.1907G>A (NM_001134363) was detected in a proband (III.1) in the described family. This mutation results in the substitution of arginine (R) for histidine (H) in a highly conserved 6 amino acid site of PRSRSP (amino acid residues 633-638) in the RS domain of the protein, p.Arg636His. A change in any of these amino acids accompanies the missense variants p.Arg636Ser and p.Arg636Cys [17, 18]. The mentioned mutations are prevalent in patients with DCMP: in the work of T.M.Hey et al. 2019, the p.Arg636His mutation was detected in 16 patients, and the p.Arg636Ser mutation in 47 patients [24]. Substitution of any amino acid of the RS domain leads to impaired interaction of Rbm20 with transporter-3 and disrupts its localization in the nucleus [25]. Mutations at each of the six RS-domain positions have now been described, and in all cases, they result in cardiomyopathy with a dominant dilated phenotype, atrial fibrillation, and a high risk of sudden cardiac death [26, 27].

The family observation we presented also demonstrates a diversity of clinical phenotypes ranging from cases of SCD, DCMP to asymptomatic forms such as in the proband's relative, III.2. The 2016 consensus document attempted to classify the phenotypic diversity of clinical forms in families with malignant mutations by introducing the term hypokinetic nondilated cardiomyopathy as an intermediate stage preceding the unfolding picture of dilated cardiomyopathy. According to this document, relatives who are mutation carriers are characterized by a preclinical phase without cardiac manifestations, which can further rapidly progress to severe impairment of the pumping function of the heart with the development of heart failure [14]. Current recommendations do not provide methods of SCD prophylaxis for asymptomatic carriers of pathogenic mutations. However, the fact of the presence of a pathogenic mutation in the context of our family observation serves as a basis for dynamic follow-up of the proband's relative - III.2. In this case, the decision on the need for the use of measures for the prevention of SCD may be reconsidered during the life of the patient.

CONCLUSION

The presented clinical observation demonstrates the diversity of clinical phenotypes due to a malignant pathogenic mutation in the *RBM20* gene in one family, ranging from cases of sudden death to mildly symptomatic forms. In addition, this case allowed us to detect for the first time the presence of QT interval prolongation due to fusion with the U wave in carriers of a malignant familial mutation. QT interval prolongation may potentially contribute further to the setting for ventricular arrhythmias and risk of SCD in patients with this rare genetic pathology.

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