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Clinical Cases

CASQ2: clinical and genetic insights into catecholaminergic polymorphic ventricular tachycardia across three families

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Catecholaminergic polymorphic ventricular tachycardia is a primary channelopathy with a high mortality rate if left untreated. In 3 to 5% of catecholaminergic polymorphic ventricular tachycardia patients, mutations in the *CASQ2* gene, either in a homozygous or compound heterozygous form, have been identified. In this article, we present a clinical case series of patients from three unrelated families with mutations in the *CASQ2* gene, including three novel mutations (p.Leu167Pro, p.Asp325GlyfsTer7, and p.Glu259Ter). All our patients with homozygous or compound heterozygous *CASQ2* gene mutations experienced a severe disease course, with early manifestations and resistance to specific anti-arrhythmic treatment, including beta-blockers. They exhibited a wide range of heart rhythm abnormalities, both ventricular and supraventricular, and had a high risk of sudden cardiac death. In all cases, ventricular heart arrhythmias persisted despite regular treatment with specific anti-arrhythmic agents, unless selective left-sided sympathectomy had been performed. The management of this patient group emphasized an individualized approach, combining medical and surgical treatment methods tailored to each patient's unique needs and condition.

Key words: catecholaminergic polymorphic ventricular tachycardia, calsequestrin, *CASQ2*, autosomal-recessive

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) belongs to the group of channelopathies and is characterized by the emergence of bidirectional or polymorphic ventricular tachycardia in response to adrenergic stimulation. The prevalence of the disease is not precisely established and is estimated to range from 1 in 10,000 to 1 in 100,000 [1, 2]. The average age of disease manifestation is 12 years [3, 4]. Currently, CPVT is recognized as a significant cause of sudden cardiac death (SCD) in children [4]. From a molecular-genetic perspective, susceptibility to the onset of unstable arrhythmia arises due to excessive accumulation of Ca^{2+} ions in the cytoplasm of cardiomyocytes [5]. The most common causes of the disease are mutations in the *RYR2* and *CASQ2* genes [6, 7]. The *CASQ2* gene encodes the cardiac isoform of calsequestrin, known as calsequestrin-2, located in the sarcoplasmic reticulum of cardiomyocytes. This protein is responsible for binding Ca^{2+} ions in the terminal cisternae of the sarcoplasmic reticulum and participates in regulating calcium release by interacting with the ryanodine receptor [7]. Mutations in the *CASQ2* gene lead to impaired ability of calsequestrin-2 to bind Ca^{2+} ions, contributing to their accumulation in the cytoplasm and the emergence of delayed

afterdepolarizations. Disruption of charge on the inner membrane of cardiomyocytes underlies proarrhythmic effects. *CASQ2* gene mutations constitute the second most common cause of CPVT, occurring in 3–5% of cases and typically being associated with a more severe disease course [3, 8].

Clinical manifestation of the disease is attributed to mutations in the *CASQ2* gene in a homozygous or compound-heterozygous state, indicating autosomal recessive inheritance. However, there are reports describing rare instances of clinical manifestation of the disease in patients with *CASQ2* gene mutations in a heterozygous state. The mechanisms leading to phenotypic expressions of the disease in patients with heterozygous *CASQ2* gene mutations are multifaceted and, in some cases, linked to peculiarities in the conformation of calsequestrin-2 protein. In such instances, the protein, incapable of dimerization, is removed from the sarcoplasmic reticulum and subsequently degraded [3, 8].

In this series of observations, we analyzed the clinical characteristics and genetic features of three families, where patients with clinical symptoms were identified to have mutations in the *CASQ2* gene, three of which have not previously been described in the literature. Two probands exhibited compound-heterozygous mutations, while one displayed homozygous mutations. The objective of this study was to analyze the disease course in CPVT patients with *CASQ2* gene mutations, three of which are novel, contributing to timely CPVT diagnosis and enhancing prognosis in this patient subset.

Materials and methods

Patients with syncope episodes and/or registered exertional polymorphic ventricular tachycardia (EPVT) were referred for evaluation to the Veltischev Research and Clinical Institute for Pediatrics and Pediatric Surgery of the Pirogov Russian National Research Medical University. Instrumental methods of investigation included electrocardiography (ECG), echocardiography, ambulatory monitoring of heart rhythm (Holter ECG), and treadmill stress testing for children older than 6 years. Patients clinically diagnosed with CPVT or suspected to have this condition were recommended to undergo molecular-genetic testing. This investigation involved performing whole exome or whole genome sequencing on probands, followed by identifying the detected mutation using Sanger sequencing in first-degree relatives. The following criteria were selected for inclusion in this study: (1) presence of a clinically established CPVT diagnosis according to current clinical guidelines, (2) presence of a mutation in the *CASQ2* gene.

The research protocol was approved by the Ethical Committee of the Veltischev Research and Clinical Institute for Pediatrics and Pediatric Surgery of the Pirogov Russian National Research Medical University (Protocol No. 2 dated February 17, 2023). The legal representatives of all patients signed written informed consent.

Detailed description of CPVT families

Family 1

Clinical evaluation of the proband and the family members

From the medical history, it is known that in two brothers (Patient 1 and Patient 2), the manifestation of the disease occurred at the age of 3 years in the form of syncope during physical exertion. The diagnosis was established based on Holter monitoring, which recorded exercise-induced bidirectional ventricular tachycardia (Fig. 1). Upon routine examination in both cases, additional findings included bradycardia and atrioventricular dissociation. Following diagnosis, specific antiarrhythmic therapy with atenolol at a dose of 1 mg/kg/day was prescribed. Medication compliance was regular and monitored by the children's parents. Due to progressive bradycardia, and with the aim of maintaining optimal beta-adrenergic blocker therapy doses, an implantation of a pacemaker was performed in both patients. Despite regular intake of antiarrhythmic therapy (atenolol at a dose of no less than 1 mg/kg/day), syncopal episodes recurred in both cases at a frequency of several times a year. Considering the occurrence

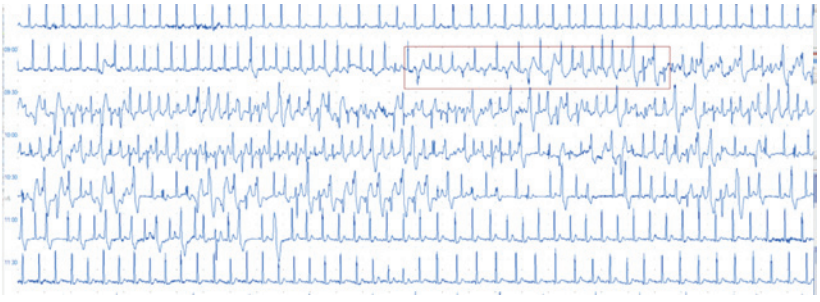

Fig. 1. A fragment of the 24-hour electrocardiographic monitoring: background sinus tachycardia with a heart rate of 121 bpm and polymorphic ventricular extrasystoles with transformation into polymorphic ventricular tachycardia (the beginning of the episode in the red frame), with subsequent bidirectional ventricular tachycardia of 6 sec duration; later on, bidirectional ventricular tachycardia gives way bigeminal ventricular extrasystoles and restoration of the sinus rhythm with a heart rate of 100 bpm

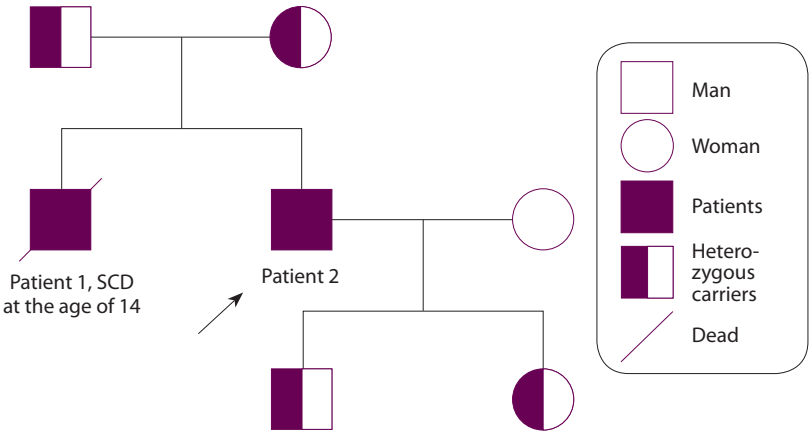

Fig. 2. The genealogy of the patients 1, 2 (family 1); SCD, sudden cardiac death

of these events, despite optimal medical therapy, implantation of a cardioverter-defibrillator (ICD) was strongly recommended for preventing SCD. However, parents declined the recommendation. SCD occurred in the older brother (Patient 1) at the age of 14 years; parents had noted increased anxiety and emotional lability in the child before the event.

Supraventricular tachycardia (ectopic atrial tachycardia and atrial fibrillation) with a heart rate of 177 bpm in Patient 2 was first detected 8 years after observation through Holter monitoring. In response, combined antiarrhythmic therapy with atenolol (1 mg/kg/day) and class IC agent, ethacizine (2 mg/kg/day), was initiated. After 17 years of combined antiarrhythmic therapy, syncopal episodes did not recur. The brothers' parents remain asymptomatic. The children of Patient 2 (a 6-year-old boy and a 1-year-old girl) also do not exhibit clinical symptoms. Hospital-based evaluations revealed isolated supraventricular premature contractions in the girl. The pedigree of Patients 1 and 2 is presented in Figure 2.

Genetic screening

Patient 2 underwent complete genome sequencing, followed by parental testing using Sanger sequencing, revealing a compound heterozygous form of the disease. In the *CASQ2* gene, a previously unreported variant, p.Leu167Pro (c.500T>C), was identified heterozygously in exon 4 out of 11 exons, leading to an amino acid substitution. This variant was detected through Sanger sequencing in the proband's mother. In the same *CASQ2* gene of Patient 2, another previously unreported variant, p.Asp325GlyfsTer7 (c.974_983del), was found heterozygously in exon 10 out of 11 exons, resulting in a frameshift and premature stop codon formation. This variant was detected through whole-exome sequencing in the proband's father, as well as in his children.

Family 2

Clinical evaluation of the proband and the family members

The girl (Patient 3) was referred to our hospital at the age of 6 years due to registered asymptomatic episodes of unstable bidirectional ventricular tachycardia according to Holter monitoring, with heart rate exceeding 160 bpm. After diagnosis establishment, specific antiarrhythmic therapy was initiated for primary prevention of life-threatening rhythm disturbances and syncopal episodes – atenolol at a dose of 1.3 mg/kg/day, subsequently titrated to 2 mg/kg/day. During beta-adrenergic blocker therapy, Holter monitoring and treadmill stress test showed frequent polymorphic single and paired ventricular extrasystoles, episodes of polymorphic ventricular tachycardia, as well as brief episodes of supraventricular (nodal) tachycardia. This prompted the addition of a second antiarrhythmic drug – propafenone – at a dose of 7 mg/kg/day. Despite regular administration of combined antiarrhythmic therapy, syncope occurred at the age of 9 years during emotional stress (while doing school homework). To prevent the development of SCD, a surgical intervention was performed – video-assisted thoracoscopic left cardiac sympathetic denervation. Over the course of two years post-surgery, no syncopal episodes were observed, and ventricular and supraventricular rhythm disturbances were not registered in control Holter monitoring and treadmill stress tests. As part of the familial cascade screening, asymptomatic relatives of the patient were evaluated. The mother and one of the brothers did not show any rhythm disturbances on Holter monitoring, including after adequate physical stress. In the youngest brother (Patient 4), Holter monitoring indicated polymorphic single and paired ventricular extrasystoles, as well as episodes of polymorphic ventricular tachycardia. Consequently, the diagnosis of CPVT was established, and specific antiarrhythmic therapy was initiated. The pedigree of Patients 3 and 4 is shown in Figure 3.

Genetic screening

Compound heterozygous variant was identified in Patient 3 through the results of whole-exome sequencing. A previously described in literature pathogenic variant c.939+5G>C was found in a heterozygous state in intron 9 out of 10 introns of the *CASQ2* gene, which leads to aberrant splicing. This variant was identified using Sanger sequencing in the child's mother. In the same *CASQ2* gene of Patient

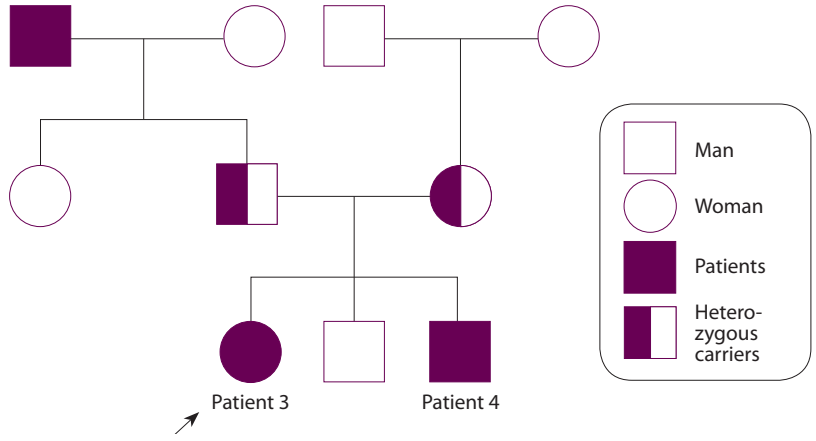

Fig. 3. The genealogy of the patients 3, 4 (family 2)

3, another pathogenic variant p.Gly127= (c.381C>T) was detected in a heterozygous state in exon 3 out of 11 exons, also resulting in aberrant splicing. This variant was confirmed using Sanger sequencing in the child's father. Sanger sequencing was performed on the proband and her younger brother (Patient 4). Two similar mutations were detected in her younger brother (Patient 4). Thus, Patient 4, like Patient 3, has a compound heterozygous disease form.

Family 3

Clinical evaluation of the proband and the family members

Patient 5 experienced his first syncope at the age of four during physical activity (running), accompanied by tonic seizures and involuntary urination. Subsequently, syncopal episodes recurred at a frequency of several times per month and were associated with both physical and emotional stress. According to the Holter monitoring data, at the age of four, mild sinus tachycardia with a heart rate of up to 122 bpm preceded the development of syncope (polymorphic ventricular extrasystoles were registered during this time). This was followed by bursts of polymorphic ventricular tachycardia with a heart rate of 231 bpm, which transformed into ventricular fibrillation and then transitioned back to polymorphic ventricular tachycardia, eventually restoring sinus rhythm. The diagnosis of CPVT was retrospectively established at the age of seven based on in-hospital examination.

In addition to ventricular rhythm abnormalities during exercise (polymorphic ventricular extrasystoles and tachycardia), other indicators were identified, including significant sinus bradycardia, shortened PQ interval, and episodes of accelerated nodal rhythm with a heart rate of 120 bpm. The patient's family history has many cases of SCD: on the father's side, the proband's grandfather died at the age of 47, great-grandfather at the age of 33, and first cousin's great-grandfather at the age of 43 (Figure 4).

Following the diagnosis, antiarrhythmic therapy with atenolol was initiated at a dose of 1 mg/kg/day, subsequently increased to 1.7 mg/kg/day. Due to episodes of accelerated nodal rhythm, propafenone was added to the therapy at a dose of 5 mg/kg/day. On regular combined antiarrhythmic therapy, no syncope or presyncope were observed. However, due to the presence of exercise-induced ventricular extrasystoles during treadmill testing at the age of 10, and considering the family history of SCD, the child underwent surgical intervention – video-assisted thoracoscopic left cardiac sympathetic denervation. After surgical treatment, syncope and presyncope were not observed for four years. The child continues to receive combined antiarrhythmic therapy with maintenance of therapeutic doses. The total observation period was 10 years.

Genetic screening

Patient 5 underwent whole exome sequencing, revealing a previously unreported variant p.Glu259Ter (c.775G>T) in a homozygous or hemizygous state in exon 7 out of 11 exons of the *CASQ2* gene. This variant results in the formation of a premature stop codon. The variant is not found in the gnomAD population frequency database and is highly likely to lead to the loss of the corresponding gene copy.

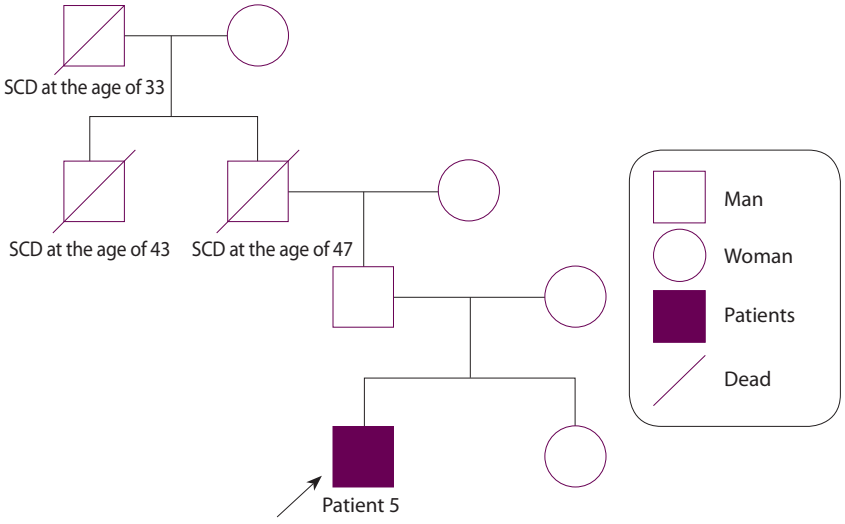

Fig. 4. The genealogy of the patient 5 (family 3); SCD, sudden cardiac death

Results

Severe disease courses were observed in 5 patients with mutations in the *CASQ2* gene in a homozygous or compound heterozygous form. The age of disease manifestation (in the form of syncope) varied from 3 to 9 years. During in-hospital examinations, 3 out of 5 patients exhibited additional electrophysiological signs of the disease, such as sinus bradycardia on Holter ECG, shortening of the PQ interval, and episodes of atrioventricular dissociation. Polymorphism of cardiac rhythm disturbances was also observed, indicating the presence of both ventricular and supraventricular rhythm disorders, such as ectopic atrial tachycardia, atrioventricular nodal reentry tachycardia, atrial fibrillation, and atrial flutter. Despite regular administration of antiarrhythmic therapy, arrhythmic events were noted in 3 out of 5 cases, indicating low effectiveness of medical treatment. One patient experienced SCD. The duration of follow-up ranged from 2 to 26 years, with an average of 11 years. Clinical and electrophysiological features of disease progression, as well as demographic data, are summarized in the table.

Discussion

It is known that mutations in the *CASQ2* gene are the second most common cause of CPVT, accounting for up to 5% of all cases [3, 8]. Clinical-genetic data on CPVT patients with *CASQ2* mutations are limited. In this series of observations, we described 5 patients from three unrelated families with CPVT carrying mutations in the *CASQ2* gene.

Heterozygous carriers remained asymptomatic and displayed no electrophysiological signs of the condition upon thorough examination. Our findings underscore the markedly severe nature of *CASQ2*-associated CPVT, aligning with existing literature [3, 7, 9]. This is evidenced by early disease onset, resistance to specific antiarrhythmic therapy using beta-blockers, a spectrum of heart rhythm aberrations (both ventricular and supraventricular), and heightened risk of ventricular arrhythmias. Within this clinical series, ventricular rhythm disturbances persisted among all patients following initiation of targeted antiarrhythmic therapy, unless selective left-sided sympathectomy was performed.

The suboptimal effectiveness of pharmacological intervention underscores the need for a personalized

Clinical and demographic characteristics of the patients

Parameter	Patient number				
	1	2	3	4	5
Gender	M	M	F	M	M
Age at manifestation, years	3	3	9	–	4
Bradycardia	+	+	–	–	+
Short PQ interval	+	+	–	–	+
Atrioventricular dissociation	+	+	–	–	+
Supraventricular arrhythmias	AF, atrial flutter	EAT, AF	AVNRT	–	AVNRT
Syncope	+	+	+	–	+
Sudden cardiac arrest	+	–	–	–	–
Cardiac events despite beta-blockers treatment	+	+	+	–	–
Sudden cardiac death	+	–	–	–	–
Follow-up, years	11	26	6	2	10

AF, atrial fibrillation; AVNRT, atrioventricular nodal re-entry tachycardia; EAT, ectopic atrial tachycardia; F, female; M, male

treatment approach within this patient cohort. Given the elevated risks of life-threatening conditions and the limited efficacy of beta-blocker therapy, the presence of *CASQ2* gene mutations in a homozygous or compound-heterozygous form should be regarded as an additional factor influencing the consideration of operative intervention – specifically, left cardiac sympathetic denervation, the effectiveness of which continues to be substantiated [10–13]. Timely cardioverter-defibrillator implantation contributes to the mitigation of ventricular arrhythmia risk [14, 15].

In the presented case series, each child with an observation period exceeding 3 years not only exhibited ventricular rhythm disturbances, but also experienced episodes of ectopic supraventricular tachycardia. Previous studies have indicated that supraventricular rhythm disturbances, such as atrioventricular focal atrial tachycardia, atrial fibrillation, and atrial flutter, can serve as triggers for ventricular rhythm disturbances in CPVT patients, including polymorphic and bidirectional ventricular tachycardia [16].

The polymorphism of rhythm disturbances is presumed to stem from alterations in the electrophysiological properties of not only ventricular cardiomyocytes but also atria [17]. To prevent the emergence of supraventricular rhythm disturbances, which in some cases acted as triggers for ventricular rhythm disturbances, combined antiarrhythmic therapy was administered. It is well established that combined antiarrhythmic therapy aims to control both supraventricular and ventricular rhythm disturbances in CPVT patients [18]. For instance, in 2017, a randomized placebo-controlled clinical trial conducted by P.J. Kannankeril et al. demonstrated that the addition of flecainide to beta-blocker treatment significantly reduces the risk of exertion-related ventricular arrhythmias in CPVT patients, thus potentially contributing to the mitigation of arrhythmogenic events [19]. The body of evidence supporting the efficacy of flecainide continues to grow [20, 21]. Another agent that reduces the occurrence of proarrhythmic calcium currents in cardiomyocytes and holds potential efficacy in CPVT patients is propafenone [22, 23].

To determine the effectiveness of adding class IC antiarrhythmic drugs to the therapy of patients with *CASQ2* gene mutations and whether expanding indications for combined antiarrhythmic therapy is appropriate for this patient subset, further research is warranted. The question of whether specific antiarrhythmic therapy should be prescribed to asymptomatic relatives of the proband – carriers of heterozygous *CASQ2* gene mutations – remains open. According to data from various studies, carriers of heterozygous mutations may develop characteristic clinical symptoms and, in certain instances, require treatment [3, 8, 9].

The spectrum of disturbances can vary from ventricular rhythm disruptions as observed during treadmill tests to the development of SCD. The age of disease manifestation also displays wide variability, emphasizing the necessity of conducting investigations, such as treadmill tests, upon the identification of heterozygous *CASQ2* mutations [8]. The likely molecular basis for clinical manifestations in patients with heterozygous *CASQ2* mutations involves a disruption in the conformation of the calsequestrin-2 protein. Alterations in the formation of the protein's quaternary structure lead to its displacement from the sarcoplasmic reticulum [8].

In our study, relatives of patients with confirmed heterozygous *CASQ2* mutations remained asymptomatic and displayed no ventricular rhythm disturbances according to 24-hour Holter monitoring. However, the patient's family history marked by a high concentration of SCD cases raises the question of disease manifestation in heterozygous *CASQ2* mutations. Despite this, attributing the exact cause of death was challenging. Further investigation into the likelihood of clinical manifestations upon the detection of *CASQ2* gene mutations in heterozygous state will contribute to enhancing the quality of CPVT diagnosis and refining the accuracy of predicting arrhythmogenic risks in both CPVT patients and asymptomatic relatives.

Conclusion

Within the presented cohort of patients with homozygous or compound-heterozygous *CASQ2* gene mutations, a severe disease course prevailed, evident through early pathology manifestation, polymorphic rhythm disturbances, and a notable resistance to medical therapy. Control of supraventricular rhythm disturbances through combined antiarrhythmic therapy and timely interventions like left-sided sympathectomy, and for some patients, cardioverter-defibrillator implantation, were essential to prevent life-threatening conditions and improve the prognosis of this patient group. Further exploration of disease course peculiarities in CPVT patients associated with *CASQ2* gene mutations will contribute to developing personalized management algorithms for this patient subset.

Additional information

Conflict of interests

The authors declare no conflict of interests.

Authors' contribution

Both authors have equally contributed to the manuscript. Both authors have read and approved the final version of the manuscript before submission, agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved.

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CASQ2: клинико-генетические особенности катехоламинергической полиморфной желудочковой тахикардии в трех семьях

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Катехоламинергическая полиморфная желудочковая тахикардия относится к первичным каналопатиям и в отсутствие лечения характеризуется высоким уровнем летальности. Мутации в гене *CASQ2* в гомозиготной или компаунд-гетерозиготной форме выявляются у 3–5% больных с катехоламинергической полиморфной желудочковой тахикардией. Мы представляем серию клинических наблюдений больных из трех неродственных семей с мутациями в гене *CASQ2*; три мутации (p.Leu167Pro, p.Asp325GlyfsTer7 и p. Glu259Ter) описаны нами впервые. У всех наших пациентов с мутациями в гене *CASQ2* в гомозиготной или компаунд-гетерозиготной форме отмечалось тяжелое течение заболевания: ранняя манифестация, резистентность к специфической антиаритмической терапии бета-адреноблокаторами, полиморфизм нарушений сердечного ритма (наличие как желудочковых, так и наджелудочковых нарушений ритма), высокий риск развития внезапной сердечной смерти. Сохранение желудочковых нарушений сердечного ритма, несмотря на регулярный прием специфической антиаритмической терапии, отмечено во всех случаях, когда не была выполнена селективная левосторонняя симпатэктомия. Индивидуализированный подход к выбору медикаментозных и оперативных методов лечения был краеугольным камнем в ведении данной группы больных.

Ключевые слова: катехоламинергическая полиморфная желудочковая тахикардия, кальсеквестрин, *CASQ2*, аутосомно-рецессивная форма

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