DOI: 10.24412/2311-1623-2024-44-4-15

A systematic approach to the diagnosis of hereditary arrhythmias: current trends and practical recommendations

Iskenderov B.G.,[1] Lokhina T.V.[1, 2], Burmistrova L.F.[2], Berenshtein N.V.[1]

[1] Penza Institute for Advanced Medical Education — Branch of Russian Medical Academy of Continuing Professional Education, Penza, Russia.
[2] Penza State University, Penza, Russia.

AUTHORS

Bakhram H. Iskenderov*, MD, PhD, Head and the Professor of the Department of Therapy, Cardiology, Functional Diagnostics and Rheumatology, Penza branch of the Russian Medical Academy of Continuing Professional Education of the Ministry of Health of Russia, Penza, Russia. ORCID: 0000-0003-3786-7559

Tatiana V. Lokhina, MD, PhD, Professor of the Department of Therapy, Cardiology, Functional Diagnostics and Rheumatology, Penza branch of the Russian Medical Academy of Continuing Professional Education of the Ministry of Health of Russia, Penza, Russia. ORCID: 0000-0002-9493-444X

Larisa F. Burmistrova, MD, PhD, Associate Professor, Head of the Department of Polyclinic Therapy and Mobilization Training in Healthcare, Penza State University; Penza, Russia. ORCID: 0000-0002-6568-0305

Natalya V. Berenshtein, MD, PhD, Assosiate Professor of Department of Therapy, Cardiology, Functional Diagnostics and Rheumatology, Penza branch of the Russian Medical Academy of Continuing Professional Education of the Ministry of Health of Russia, Penza, Russia. ORCID: 0000-0002-1589-2799.

This review article discusses the current aspects of diagnosis of hereditary cardiac arrhythmias, current clinical practice, potential difficulties and medical errors in the detection and management of patients with presumed primary electrical heart disease (channelopathies). It should be noted that in the available literature there are single reports devoted to a detailed analysis of the possible causes of delayed or erroneous diagnosis of channelopathies in real clinical practice. Given the high risk of sudden arrhythmic death, which is often the early and first manifestation of hereditary arrhythmia syndromes, their timely diagnosis, implementation of therapeutic and preventive measures in the proband and family members of the first degree of kinship are the most important tasks of the preventive strategy of high cardiovascular risk. These circumstances emphasize the clinical significance of a systematic diagnostic approach in the diagnosis/suspicion of hereditary arrhythmias and compliance with clinical guidelines for the diagnosis and prevention of sudden cardiac death in clinical practice.

Keywords: sudden cardiac death, channelopathies, hereditary arrhythmias, genetic testing, long QT syndrome, Brugada syndrome

Conflict of interests: none declared.

* Corresponding author. Тел./Tel. +7 (906) 399-5672. E-mail: iskenderovbg@mail.ru

International Heart and Vascular Disease Journal. Volume 12, № 44, December 2024
ISSN: 2311-1623 (Print)
ISSN: 2311-1631 (Online)
http://www.heart-vdj.com

Recieved: 01.10.2024
Accepted: 02.12.2024

For citation: Iskenderov B.G., Lokhina T.V., Burmistrova L.F., Berenshtein N.V. A systematic approach to the diagnosis of hereditary arrhythmias: current trends and practical recommendations. International Journal of Heart and Vascular Diseases. 2024. 12(44):4-15. DOI: 10.24412/2311-1623-2024-44-4-15

Introduction

Hereditary arrhythmias account for more than half of all initially unexplained cases of sudden cardiac death (SCD) in young adults [1, 2]. Hereditary arrhythmias are primary in 70% of cases (channelopathy) and caused by structural heart disease in 30% of cases [3, 4]. Early diagnosis of hereditary arrhythmias can significantly reduce the risk of SCD because in about 30% of cases, SCD is the first and early symptom of these diseases [1, 5]. The detectability of hereditary arrhythmias, and consequently, the effectiveness of control of sudden arrhythmic death (SAD) is also determined by the complex theoretical knowledge and practical skills of general practitioners [6]. Perhaps this explains the dissonance between the declared frequency of hereditary cardiac arrhythmias and the current real practice, which is usually reduced to the description of notable and isolated clinical episodes.

It should be noted that the wide variability of information on the prevalence of hereditary arrhythmias relies on data obtained in individual epidemiologic studies or extrapolation of their results to the general population [5, 7]. In clinical practice, as a rule, syndromal hereditary arrhythmias (Brugada, Jervell and Lange-Nielsen, Timothy, Andersen-Tawil syndromes) characterized by both cardiac and extracardiac phenotype are identified [8, 9]. However, in most cases, hereditary arrhythmias manifest non-specific signs (syncope, palpitations, seizures), and thus remain without proper attention of specialists [10]. The reason for this may be the functional risk alleles common in the population and conditionally pathogenic or weakly penetrant genetic variants, the phenotypic expression of which requires the presence of additional risk factors (RF) (medications, electrolyte disorders, fever, etc.) [11].

Hereditary arrhythmias can be caused either solely by abnormalities of cardiomyocyte ion channels (channelopathies) or they are an early manifestation of primary (idiopathic) structural heart disease [12, 13]. In addition to life-threatening ventricular tachyarrhythmias, hereditary rhythm and conduction disorders include atrial fibrillation, Wolff-Parkinson-White syndrome, sinoatrial or atrioventricular block, etc.

It should be noted that over the last 20 years, the availability of high-tech medical care for patients with cardiovascular diseases in the Russian Federation has significantly improved. As a result, the frequency of implantation of cardioverter-defibrillators and pacemakers, as well as ablation therapy has increased significantly [13]. This dictates the importance of organizing a coordinated structure of specialized medical and genetic care for the population, including patients with potential hereditary arrhythmias.

In view of the above, it is of particular interest to highlight the following topical aspects of hereditary arrhythmias:

- recognizing the signs and RF that should raise suspicion of hereditary arrhythmia syndrome;
- outlining the reasons for erroneous or delayed diagnosis of hereditary arrhythmias;
- listing the difficulties and limitations of interpreting genetic studies.

It should be noted that a detailed analysis of the difficulties in the diagnosis of hereditary arrhythmias associated with known limitations or erroneous interpretation of the results of studies will improve the efficiency of medical and genetic care for patients with suspected channelopathies. Information was searched in international databases such as PubMed, Scopus, Web of Science and Cochrane Library, as well as in Russian databases, including eLibrary.

Prevalence of hereditary arrhythmias in the population

It should be noted that the data on the prevalence of individual cardiac channelopathies in the general population are the results of international multicenter registry studies, based on which electronic information databases are created that take into account ethnic, racial, and geographical specifics of the distribution of individual variants of hereditary arrhythmias [1, 5, 11]. For example, in European and

DOI: 10.24412/2311-1623-2024-44-4-15

North American populations, Brugada syndrome (BrS,) occurs from 0.012 % to 0.26 %, whereas in endemic areas of southeast Asia (Japan, Thailand, Laos, Philippines) it is much higher and ranges from 0.7 % to 1.0 % [14, 15]. The prevalence of Jervell and Lange-Nielsen syndrome worldwide ranges from 1 to 6 per 1 million population, and in Scandinavian countries it is 1 per 200,000 population [16, 17].

The dispersion in the detection of cardiac channelopathies can also be explained by the wide genetic heterogeneity of individual populations and the influence of external factors [11]. Thus, it was shown that the prevalence of short QT syndrome (SQTS) with a QTc interval ⩽300 ms had the highest frequency per 100,000 people in African Americans (5.8), followed by Caucasians (3.2), Hispanics (1.8), and Asian and Pacific Islanders (1.6) [5].

The heterogeneity of access to genetic testing in different countries also affects the diagnosis of cardiac channelopathies [10, 18]. Careful collection of family history (preferably three generations) is essential to identify patients and affected family members. The absence of clinical manifestation of an underlying hereditary disease (asymptomatic course) tends to reduce the real population frequency of hereditary arrhythmias. The prevalence of cardiac channelopathies is also affected by incomplete penetrance of mutations of the gene responsible for the development of the disease [11]. For example, in 40% of genotyped cases of long QT syndrome (LQTS), QT intervals are within normal limits [19, 20]. Therefore, most experts believe that the estimated prevalence of hereditary arrhythmias in the population may be higher than the existing statistics [5, 11]. According to epidemiologic studies, the prevalence of LQTS, BrS, and catecholaminergic polymorphic VT (CPVT, catecholaminergic polymorphic ventricular tachycardia) individually is about 1:2000. The rarest inherited arrhythmia is SQTS, with an incidence ranging from 1:1000 to 1:10,000 in the population [21].

The prevalence of LQTS and SQTS in the population, along with other factors, is influenced by methodologic errors associated with QT interval measurement on standard ECG [20, 22]. For this purpose, manual QT interval measurement is considered the optimal method. Determination of diagnostic thresholds for shortening or lengthening of the QT interval is an important ECG pattern of LQTS and SQTS, as in BrS the presence of ECG pattern type 1 [9, 20, 23]. On the other hand, the widespread use of pharmacologic provocation with sodium channel blockers in suspected BrS (BrS ECG patterns type 2 or 3) caused drug-induced electrocardiographic "brugadophobia". In this regard, it was reported that in Europe, 70% of asymptomatic patients with BrS were "diagnosed" after a positive ajmalin test [15].

Clinical approach to the diagnosis of cardiac channelopathies

The key components in establishing the diagnosis of channelopathies are a careful evaluation of presenting symptoms, a systematic search for relevant anamnestic data, and an informed approach to diagnostic procedures [2, 12]. Because affected patients may first consult their family physicians, pediatricians, or neurologists, it is critical that all physicians, not just cardiologists, are aware of and able to identify the signs of hereditary arrhythmias [6, 10]. A detailed pedigree of at least three generations should be compiled. History of syncope, arrhythmias, pacemaker implantation, indication of seizures, presence of repeated abortions and early unexplained sudden death or any other cardiac disease should be identified in all family members of the first degree of consanguinity [4, 24].

Systematic collection of medical history, along with other factors, is an important condition for timely diagnosis of hereditary arrhythmias. Manifestation of the disease, manifested by clinical symptoms and the presence of complaints, contributes to the detection of symptomatic patients more often and earlier than asymptomatic patients [2, 13]. The most frequent and formidable manifestations of hereditary arrhythmias are syncope, seizures and sudden death due to certain triggers. Syncope is considered one of the most difficult dilemmas for the clinician because, on the one hand, it can be as innocent as vasovagal syncope and, on the other hand, as fatal as syncope associated with polymorphic VT or VF [25]. Syncope is such an integral part of neurological and cardiological practice that specialized clinics often establish syncope units to comprehensively examine patients and identify possible causes of syncope.

In some channelopathies, arrhythmogenesis can be manifested by different types of ventricular arrhythmias, which have differential diagnostic value. For example, LQTS is most characterized by polymorphic VT of the torsades de pointes (pirouette) type; in

BrS it is polymorphic VT [26, 27]. In CPVT, bidirectional VT characterized by alternating polarity of leading QRS [28] is observed, and in arrhythmogenic cardiomyopathy (CMP) of the right ventricle, monomorphic VT of the left bundle branch block type is observed. These arrhythmias often resolve spontaneously, but can transform into VF. During an arrhythmia attack, patients often experience generalized symptoms such as palpitations, dizziness, paroxysmal dyspnea, chest pain and abrupt weakness, as well as fear or panic.

Importantly, syndromal variants of hereditary arrhythmias reveal extracardiac, multisystem lesions in addition to the cardiac phenotype, which can both aid in the correct diagnosis of the genetic disease and lead to inappropriate patient management. For example, a prolonged QT interval and congenital bilateral sensorineural deafness are characteristic of Jervell and Lange-Nielsen syndrome [9, 17], and facial dysmorphism and syndactyly are characteristic of Andersen-Tawil syndrome [29].

Analysis of possible triggers for arrhythmias often provides a basis for suspicion of underlying pathology in many channelopathies. Triggers often differ depending on the variant of inherited arrhythmia and can aid diagnosis [2, 12]. For example, an arrhythmic event occurring during physical exertion, especially swimming, suggests LQT1 type, while arrhythmic syncope associated with sudden loud auditory stimuli is more characteristic of LQT2 type. Since physical and emotional stimuli are physiologically associated with increased release of catecholamines into the blood, the occurrence of syncope in such situations is characteristic of CPVT [13, 28]. Arrhythmic events occurring during sleep or rest, as well as against the background of fever, indicate LQT3 or BrS type [14, 16].

It should also be noted that almost all hereditary arrhythmias have incomplete penetrance (less than 100% of cases), and therefore, even if the genotype is identical, the phenotype of the disease may differ within a family [11]. Penetrance for individual channelopathies depends on biological sex. For example, the diagnosis of SQTS or BrS based on clinical symptoms is established predominantly in male patients [22, 23]. In addition, carriers of SQTS mutations showed shorter QTc intervals compared to non-carriers. This allows differentiating between shortened QT interval (so-called "benign" variant) and SQTS [14, 21]. Gene penetrance, both gene expression and genotype-phenotype correlation differ between proband and relatives carrying a mutation of the same gene [11]. Thus, the probability of diagnosis of cardiac channelopathies also depends on the variability of expression and penetrance of the disease.

Alternative diagnoses requiring differential diagnosis in hereditary arrhythmias

Difficulties in clinical diagnosis of hereditary arrhythmias are due to non-specific symptomatology, in some cases the absence of ECG pattern and the prevalence of latent (asymptomatic) forms [17, 30]. Given that symptomatic patients with hereditary arrhythmias often have recurrent syncope due to VT or VF, they can be observed for a long time with the diagnosis of "epilepsy" and receive anticonvulsant therapy without effect, remaining in the high-risk group of SCD [2, 25]. At the same time, diagnosis is possible only by genetic test [18].

The most common alternative diagnoses for hereditary arrhythmias are seizure disorder, atypical febrile seizures, and sudden infant death syndrome in children with undiagnosed channelopathy [3, 7, 25]. Therefore, a detailed family history and ECG analysis are mandatory in all patients with an electroencephalographically negative seizure disorder, in young children with atypical seizures during fever, and in family members of first-degree relatives of cases of sudden infant death.

It should be noted that arrhythmogenic syncope often has to be distinguished from an epileptic seizure. An epileptic seizure is usually prodromal, with precursors (auras) of syncope, whereas arrhythmogenic syncope is non-prodromal [13]. In addition, in cases of interrupted cardiac arrest, syncope does not last long, seizures rarely occur, and the person usually feels relatively satisfactory after syncope. However, in most cases of epilepsy, prolonged and generalized tonic-clonic seizures are observed, and after the seizure, patients report abrupt weakness, collapse, and possible tongue biting [25].

It has been retrospectively shown that epilepsy-like seizures triggered by cardiac arrhythmias are the most common cause of late diagnosis of channelopathies and may be misinterpreted as epilepsy [1, 9]. For example, in a cohort of patients with LQTS, abnormal electroencephalograms were detected in 71%

DOI: 10.24412/2311-1623-2024-44-4-15

of cases compared to 13% of controls (p<0.01) [16]. Careful examination of these patients did not reveal any other possible cause other than mutation of the KCNQ1 gene responsible for LQT1. The KCNQ1 gene encoding the potassium channel is known to be expressed not only in the heart but also in the forebrain and brainstem [11, 20].

Life-threatening cardiac arrhythmias are known to occur in a significant proportion of generalized seizure attacks and represent a possible pathophysiological mechanism for the association of unexplained sudden death and epilepsy [25]. Consequently, individual patients diagnosed with epilepsy may have concomitant hereditary arrhythmias and be at particularly high risk of fatal arrhythmias associated with an epileptic seizure [25]. Therefore, information about sudden death in the family of a patient with an unusual convulsive seizure should prompt a thorough cardiologic evaluation.

In pediatric practice, observed primary periodic paralysis or neuromuscular channelopathies also merit attention with respect to cardiac channelopathies [7]. For example, in patients with Andersen-Tawil syndrome (classic type LQT7), hypokalemic periodic paralysis is almost always seen, and often occurs against a background of prolonged generalized weakness and proceeds without myotonic manifestations [29]. Episodes of muscle weakness manifest usually before the age of 10 years or during adolescence. During the time between attacks, such children do not present any complaints.

ECG patterns of hereditary arrhythmias

It should be noted that frequent manifestations of the cardiac phenotype of channelopathies are ECG changes, including various rhythm and conduction disorders. ECG patterns specific for certain types of hereditary arrhythmias play an important role in the diagnosis of these conditions [2, 7]. Therefore, resting 12-lead ECG recording is an integral part of the evaluation of a suspected case of channelopathy. A systematic analysis of all aspects of the ECG should be performed, as atrial and/or ventricular depolarization and repolarization abnormalities may coexist [26].

The basis for the diagnosis of LQTS with a high probability, according to the LQTS diagnostic scoring scale, is a QTc interval ≥500 ms on repeated standard ECGs and in the absence of secondary causes of QT interval prolongation [17, 20]. A similar requirement for the diagnosis of SQTS is a QTc interval ≤330 ms [21], and for the diagnosis of BrS is the registration of a spontaneous ECG pattern type 1 in leads V1-V3 [23]. However, they represent extreme deviations of QTc intervals, which may lead to hypodiagnosis of LQTS and SQTS in more moderate cases.

Abnormal changes in the standard resting ECG with no other explanation may be suspicious for cardiac channelopathies:

- prolonged/shortened QT/QTc interval;
- ventricular extrasystoles occurring during an exercise stress test;
- oblique descending or saddle-shaped ST-segment elevation in leads V1-V3;
- alternation of the T-wave (negative or abnormal T-wave);
- slowing of cardiac conduction (sinoatrial, atrioventricular, and intraventricular block);
- registration of epsilon wave on ECG in leads V1–V3;
- pronounced U-wave, prolonging the QT-U interval, in the precardiac leads;
- pronounced J-wave manifested with or without ST segment elevation, especially in posterior or posterolateral leads of the ECG;
- isolated prolongation of PR interval;
- depression of the PQ (PR) segment in the lower leads of the ECG.

It should be noted that certain types of LQTS have characteristic ECG patterns of the T-wave. For example, LQT1 is characterized by a broadened T, while in LQT2 the T is usually bifurcated and low-amplitude. In LQT3, QT interval prolongation is explained by ST segment prolongation, and the T-wave has a normal configuration [31]. Taking into account personal and family history, this may help in determining the indications for genetic testing [27].

Limitations of interpreting a standard resting ECG

Despite the availability and sufficient informativity of standard resting ECG, this method has limitations in almost all types of channelopathies. For example, there are difficulties with accurate measurement of the QT interval, which negatively affects the frequency of detection and timeliness of diagnosis of LQTS and SQTS [20]. The reasons for this are abnormalities of

ST-T morphology (biphasic, low-amplitude or inverted T-wave) caused by bundle branch block, electrolyte imbalance (hyper- and hypokalemia), ventricular hypertrophy, digitalis effect, etc. [8].

The optimal way to determine the QT interval is its manual measurement in the II lead of a standard ECG at rest and at a heart rate (HR) of 60 to 100 beats per minute [17, 20]. In this case, the tangential method is the most accurate, when the end of the T-wave is determined by the intersection of a tangent line drawn from the steepest point of the T-wave slope with the isoelectric line. To level the influence of HR on the QT interval, it is corrected for HR (QTc) using mathematical formulas, of which the most commonly used is the Bazett formula. It has been shown that even experts measure the QT interval during LQTS with an error of 10 to 70 ms [20]. A study of the prevalence of SQTS based on the analysis of more than 6.3 million ECG recordings in 1.7 million people [22], automatic ECG analysis revealed 1086 cases with a QTc interval ⩽300 ms, while manual QT interval measurement confirmed QTc ⩽300 ms in only 45 episodes.

It has been shown that registration of pronounced U-wave in precordial leads of ECG in Andersen-Tawil and ankyrin-B syndromes mimics QT-U interval prolongation, and exclusion of U-wave from QT interval calculation almost always shows normal or borderline QT intervals [9, 29]. Therefore, there is still debate as to whether ankyrin-B and Andersen-Tawil syndromes are "typical" forms of LQTS [17].

Grounds for suspicion of channelopathies

Based on the results of the initial patient examinations, it is determined whether there are grounds for suspicion of various hereditary arrhythmias if structural causes have been ruled out.

Grounds for suspicion of LQTS:

- prolonged QT interval - in men QT ⩾440 ms and in women QT ⩾460 ms;
- standardized extensive family history positive for syncope, seizures, SCD;
- abnormalities of the T-wave (jagged, dilated, biphasic, negative);
- ECG-documented episode of pirouette-type VT;
- history of an index patient, i.e., a proband whose illness was the basis for collecting a family history for syncope, seizures, and palpitations;
- a pathologically prolonged QTc interval during stress or exercise;
- presence of arrhythmias in the context of specific triggers (e.g., swimming, loud noises, medication, hyperthermia).

Basis for suspicion of CPVT:

- index patient history (occurrence of syncope, seizures, and palpitations in response to adrenergic stimulation);
- normal resting ECG or may have marked bradycardia, atrial arrhythmias including multifocal atrial tachycardia;
- the presence of a family history of syncope, seizures, and SCD;
- the occurrence of frequent polymorphic ventricular extrasystoles during a stress test.

Grounds for suspicion of BrS:

- ECG patterns of BrS type 1, 2, or 3;
- family history positive for syncope, seizures, and SCD;
- index patient history: presence of syncope, seizures and palpitations;
- arrhythmias due to specific triggers (hyperthermia, heavy meals, alcohol consumption).

Additional methods of investigation

If clinical evaluation results suggest that a specific channelopathy is suspected, further investigations, including genetic testing for confirmation, should be performed (Figure 1). Thus, cases of sudden death at a young age in relatives, syncope, documented arrhythmias, or atypical epilepsy in the context of specific triggers should prompt further investigation.

Exercise stress test

In patients with symptoms suggestive of channelopathies and an apparently normal resting ECG, an exercise stress ECG may be performed. Given that about 40% of LQTS cases have a normal QT interval on resting ECG, it is suggested that the QT/QTc interval response to exercise should be evaluated [8, 16]. Whereas, in LQT2 and LQT3 types, the QTc interval is physiologically shortened, patients with LQT1 type have a paradoxical prolongation of the QTc interval [32]. In patients with LQTS, the lie-to-stand test or low-dose adrenaline infusion test is also recommended, although they are inferior to the stress stress test [9]. The appearance of mono- or polymorphic VT during the stress test, which disappears during the recovery phase, is a classic sign of CPVT [28]. It is important to achieve the necessary level of stress, i.e., a rapid

DOI: 10.24412/2311-1623-2024-44-4-15

increase in HR during exercise is more likely to cause VT [13]. It is not uncommon to observe ventricular allorrhythmia during exercise against the background of relatively low HR (100-110 per min), which can turn into VT [28].

hereditary arrhythmias [2, 13]. It is also necessary to identify various triggers of arrhythmic events. It should be noted that the spontaneous BrS ECG pattern can be intermittent or non-permanent. Thus, it has been shown that the reproducibility of BrS type 1

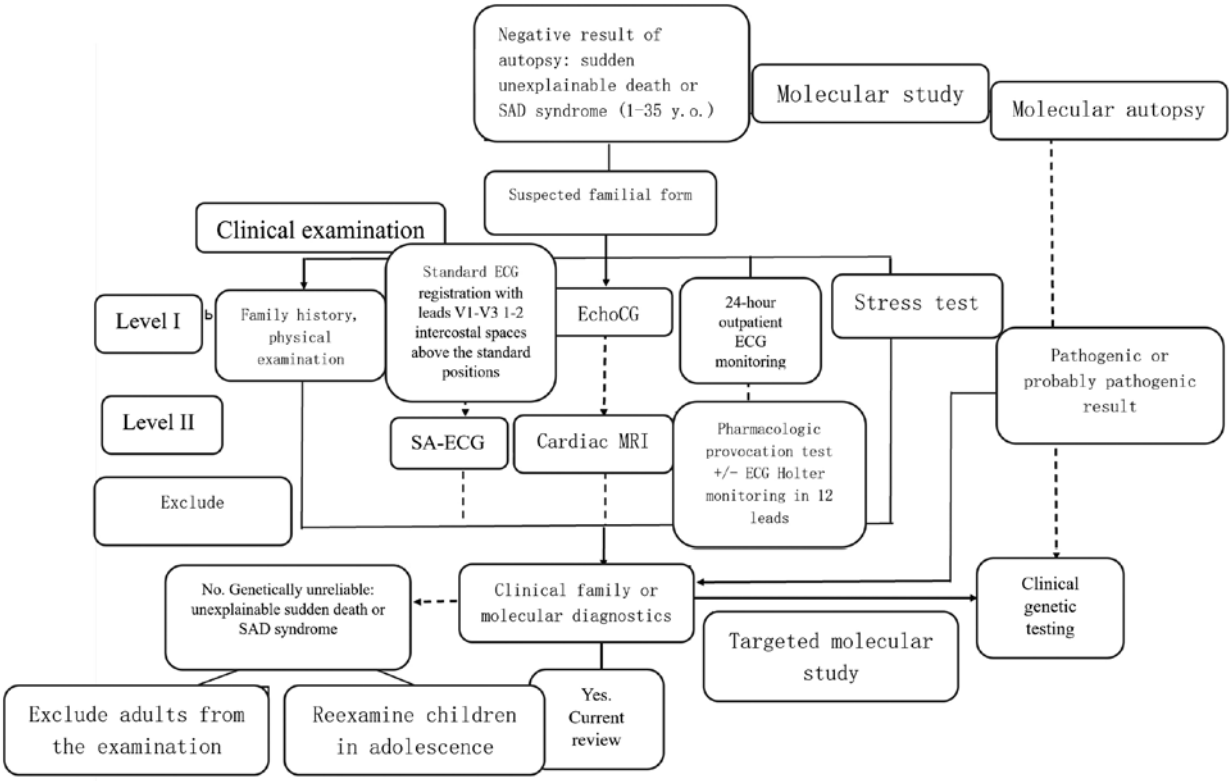

Fig. 1. The scheme of two-stage examination of probands and their family members with suspected hereditary arrhythmias

Registration of high right precordial ECG leads.

It has been shown that registration of leads V1–V3 1–2 intercostal spaces above the standard positions in case of saddle-shaped ST-segment elevation can reveal the hidden BrS ECG pattern type 1 [23]. Echocardiographic determination of registration levels of leads V1-V3, corresponding to the anatomical localization of the right ventricular outflow tract, increases the frequency of registration of diagnostic ECG pattern BrS type 1 in comparison with the standard technique: 100% vs. 43% ($p<0.001$) [15]. Additional criteria for ECG pattern BrS, such as Corrado index for ECG pattern type 1 and ß angle measurement for type 2, are also recommended [26].

Holter ECG monitoring

Is important to detect underlying cardiac rhythm and conduction abnormalities in patients with suspected ECG pattern in repeated ECG recordings is only 25% [15]. Therefore, ECG Holter monitoring can help to detect the dynamic ECG pattern of BrS type I, and thus eliminate the need for pharmacologic provocation. In cases of suspected arrhythmic syncope, implantation of a cardiac monitor is sometimes used, allowing ECG monitoring for 6 months to two years to detect heart rhythm disturbances or potential causes of syncope [13].

Electrophysiologic study (EPS)

In most cases of channelopathies, the use of cardiac EPS to induce VT has no proven benefit and, therefore, is currently not a standard diagnostic method [2]. It has been shown that the prognostic value of a positive result of EPS is 37-50%, and that of a negative result - 46-97% [13]. The possibility of VT induction during EPS using a less aggressive mode of electrical stimulation (one or two extrastimuli) in-

creases the prognostic value of the method. Cardiac EPS is mainly recommended to stratify the risk of arrhythmic events, to determine the indications for implantation of a cardioverter-defibrillator in asymptomatic patients, and to assess the efficacy of drug or ablation therapy [32]. It should be noted that failure to induce VT does not necessarily indicate a low risk of arrhythmia, especially in patients with clinical signs of high risk.

Pharmacologic provocation test

If no other diagnosis is established and the characteristics of SCD can match BrS, provocation tests with class I antiarrhythmic drugs (ajmaline, flecainide, procainamide) in first-degree relatives with structurally normal hearts are recommended [26]. Different prescribing protocols are used for each drug. After intravenous administration of the drug, a standard ECG recording or 12-lead ECG Holter monitoring with high precordial leads V1-V3 is performed to evaluate the BrS type 1 ECG pattern. Ajmaline has been shown to produce significantly more positive results than procainamide or flecainide [23]. Despite its high sensitivity, the ajmaline assay is less specific. For example, in patients with LQT3 type, arrhythmogenic right ventricular cardiomyopathy and r'-ST complexes in leads V1–V3, BrS type 1 ECG pattern may be induced, which has no prognostic value [17, 30]. Therefore, a positive ajmaline test does not provide any useful information about the risk of arrhythmic events in asymptomatic individuals with a non-diagnostic BrS type 2 or 3 ECG pattern [26].

Cardiac imaging

If structural heart disease is suspected, echocardiography or MRI may provide additional information. In these cases, cardiac disease with arrhythmias may be involved, particularly hypertrophic or dilated CMP or arrhythmogenic right ventricular CMP [2]. In this case, cardiac MRI with gadolinium contrast and follow-up of any evolution of the phenotype is recommended.

Diagnostic scoring scales for hereditary arrhythmias

In clinical practice, diagnostic scoring scales are used to verify the diagnosis of some types of hereditary arrhythmias, which take into account the combined value of clinical criteria: ECG characteristics, the nature of symptoms, family history and genetic test results. The validity of the scoring scale depends on the reliability of the criteria themselves. The interpretation of standard resting ECG is of great importance, in particular, the determination of QT interval duration in suspected LQTS and SQTS, differentiation of ECG pattern characteristic of BrS, as well as the analysis of QRS-T complex configuration in J-wave syndromes [17, 30].

It should be noted that the probability of diagnosis and the prevalence of LQTS and SQTS in the population depend not only on the correctness of QT interval measurement, but also on the accepted diagnostic criteria for the duration of QT intervals. For example, the threshold QT intervals for suspicion/diagnosis of SQTS vary widely from 220 to 360 ms: there is a "gray zone" for QTc between 370 and 330 ms [21, 22]. These difficulties are addressed by the LQTS and SQTS diagnostic scales, in which different QT interval values are assigned different scores depending on the suspision/probability of the diagnosis. For example, the modified SQTS diagnostic scoring scale assigns 1 point for a QT interval <370 ms, 2 points for a QT interval <350 ms, and 3 points for a QT interval <330 ms [21]. Evaluation of the proposed diagnostic criteria for SQTS showed that 95% of cases would receive a diagnostic score indicating a high probability of SQTS [22].

It should be noted that diagnostic scales are used to determine the gradations of probability of a particular hereditary arrhythmia syndrome and, if necessary, genetic testing is used. For example, the Schwartz P.J. et al. scale is used in the initial evaluation of patients with LQTS, according to which if the sum of scores is ⩽1, it indicates a low probability of LQTS, at 1.5-3 points the intermediate probability of LQTS is determined, and at ⩾3.5 points — a high probability of LQTS [17].

The HRS/EHRA/APHRS expert consensus document is used to diagnose BrS, and the Shanghai point scale is used only in cases of drug-induced ECG pattern of BrS. In addition to the ECG pattern, one of the following criteria is required to confirm the diagnosis: documented PV/polymorphic VT, syncope, SCD in a family of individuals younger than 45 years of age with a negative autopsy report, BrS type 1 ECG pattern in family members, or nocturnal agonal breathing [23]. Although the diagnostic scale criteria provide a systematic approach to the verification of hereditary arrhythmias, in cases of suspected channelopathies

DOI: 10.24412/2311-1623-2024-44-4-15

in proband family members, the value of the assessment scale will not be highly sensitive due to incomplete penetrance.

Diagnostic genetic testing

General principles of genetic testing

Modern next generation sequencing technologies allow us to study a panel of cardiac rhythm disorders including 40 genes and their mutations associated with the development of channelopathies [2, 11]. For genetic testing, it is crucial to confirm the association of the identified genetic alterations with the clinical phenotype. Therefore, the probability of a positive genetic test is highest in individuals with the highest phenotypic penetrance.

In the HRS/EHRA/APHRS (2022) expert consensus on the diagnosis and management of hereditary arrhythmia syndromes, genetic testing was recommended for probands with a clinical diagnosis and for all family members of a successfully genotyped proband (class I recommendation) (Table) [11]. Genetic tests play an important role in identifying "pre-symptomatic" or "low-symptomatic" young individuals with a genetic phenotype associated with the risk of developing SCD, allowing timely preventive interventions [19]. The strongest evidence in support of variant pathogenicity is segregation by phenotype in several family members [2].

Table. **The value of genetic testing for proband in cardiac channelopathies**

Disease	Diagnostic	Prognostic	Therapeutic
LQTS	+++	+++	+++
CPVT	+++	+	+
BrS	+	+	+
Progressive cardiac conduction defect	+	+	+
SQTS	+	+	+
Familial SSS	–	+	–
Familial AF	–	+	–
Early repolarization syndrome	–	–	–

Note. +++ recommended/indicated or useful; ++ may be recommended/may be useful; + may be considered/may be useful; – not recommended/not indicated or useful.

For all suspected diagnoses associated with cardiac channelopathies, the indications for genetic testing need to be justified. Depending on the level of evidence available, a genetic variant can be characterized as: benign; probably benign; variant of uncertain significance; probably pathogenic; pathogenic [11]. A pathogenic result confirms the clinical diagnosis and may serve as a prognostic or therapeutic landmark, as well as being important for subsequent screening of family members. With few exceptions, the variant of uncertain significance cannot be used for proband management or prognostic evaluation of asymptomatic family members [11].

The EHRA/HRS/APHRS/LAHRS expert consensus document outlines the important concept of "key genes" according to ClinGen (Clinical Genome Resource), i.e. genes that for each variant should be included in the "ideal" screening to enhance the achievement of clinically useful results [11]. The sensitivity of tests proposed for routine genetic testing for all types of LQTS and CPVT averages 65% and 60%, respectively, with SQTS averaging 40% and BrS averaging 25-30% [11, 18].

Family predicting (prognostic) genetic testing

Medical genetics continues to utilize the clinical and genealogical method. A positive genetic test in a proband provides an opportunity for cascade testing of first-degree relatives for a variant associated with the "culprit gene" in the proband [11, 13]. In general, cascade screening is recommended when the results will affect clinical management. Family members in whom a pathogenic variant is found should be clinically screened at regular intervals. If the patient's family members have not undergone genetic testing or are negative, they should also undergo regular clinical screening because there is significant phenotypic heterogeneity in the age of disease manifestation in members of the same family.

Postmortem genetic testing (molecular autopsy)

It is known that the annual incidence of SCD in the age group from 1 to 35 years is estimated from 1.3 to 2.8 per 100,000 population [53], and in 30–40% of cases autopsy does not reveal the cause of sudden death despite toxicologic and histopathologic analyses [33]. It is assumed that some of them died from SAD caused by channelopathies (e.g., LQTS, BrS, and CPVT).

According to guidelines, genetic testing of autopsy material (blood, thymus, spleen, liver) is indicated in all cases of SCD when inherited diseases are

suspected [11], and cascade (mutation/pathogenic variant-specific) genetic testing in first-degree family members is recommended if a pathogenic or likely pathogenic variant is identified [34]. This is particularly relevant given that most inherited diseases are inherited in an autosomal dominant pattern, meaning a 50% chance of surviving family members inheriting the same disease substrate [12]. A standard molecular autopsy panel typically includes 4 major genes that account for the majority of previously unexplained SCD cases, including KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3 / BrS1), and RYR2 (CPVT1) [11].

Molecular autopsy results were reported in 113 cases of unexplained sudden death, and pathogenic variants were identified in 27% of cases [33]. Lahrouchi N. et al. [34] studied the diagnostic value of molecular autopsy and clinical genetic study in 302 members from 82 families. They showed that the combination of molecular autopsy and clinical evaluation of surviving relatives increased the probability of detecting a pathogenic variant from 28% to 49%, and the additional independent result of molecular autopsy was 13%.

Problems of interpreting genetic test results

Selection of a panel of genetic tests and interpretation of genotyping results require a high level of specialized knowledge and a multidisciplinary approach [11]. The identification of a pathogenic variant increases the risk of a phenotype but does not equate to a clinical diagnosis. Also, a negative genetic test result never excludes a valid clinical diagnosis. If the result is positive, its plausibility must be verified, as it may turn out that the identified mutation is not the cause or the sole cause of the disease.

Choosing the right test for genotyping can be difficult due to the repetition of phenotypes and genetic heterogeneity, whereby a similar phenotype may be caused by mutations in different genes (overlap syndrome) [11]. On the other hand, the same mutation can lead to different phenotypes even in the same family (variable expressivity): for example, family members with the same *SCN5A* gene mutation may have different phenotypes, such as BrS, LQTS, and cardiac conduction abnormalities [18].

Without a presumptive diagnosis, it does not make sense to perform a general genetic test to screen every known gene associated with SCD. Such screening often detects variants/mutations that were not the cause of the disease in a particular case and can easily lead to misdiagnosis. Even with a presumptive diagnosis, sometimes the results cannot be correctly interpreted without genetic and clinical investigation of relatives. The identification of a large number of minor genes responsible for multiple variants increases the uncertainty of interpretation.

Difficulties in interpreting the results are also associated with the identification of a frequent genetic variant (polymorphism) that mostly corresponds well to the phenotype but does not explain the severity of the disease [11]. Therefore, several years later it may turn out that the identified mutation was in fact an irrelevant polymorphism. It should be noted that genetic variants in sudden death in the young often remain as variants of uncertain significance for many years, making their management difficult. However, some of them may rapidly convert to likely pathogenic variants after careful screening. Because of the age-related penetrance of a number of hereditary arrhythmias, it is recommended that children be reexamined in adolescence or early adulthood.

Conclusion

Thus, these data indicate the absence of systematic diagnostic strategies in patients with hereditary arrhythmias in real clinical practice, as well as the low level of knowledge of general practitioners on the management of these patients. A comprehensive approach to solving these problems includes the implementation of educational programs on hereditary arrhythmias for physicians of different specialties, combining the efforts of various medical institutions to create an information database of patients, as well as the creation of additional specialized centers and/or cardiogenetics departments that coordinate the work to provide high-tech medical care to affected patients and their families. Strict adherence to current clinical recommendations by physicians of specialized specialties, ensuring an interdisciplinary approach to the management of patients with hereditary arrhythmias, and stimulating the promotion of medical and social knowledge on hereditary diseases and sudden death also play an important role.

Conflict of interests: none declared.

References

1. Behr ER, Scrocco C, Wilde AAM, et al. Investigation on sudden unexpected death in the young in Europe: results of the European Heart Rhythm Association Survey. Europace. 2022; 24(2):331-9. DOI: 10.1093/europace/euab176
2. Conte G, Scherr D, Lenarczyk R, et al. Diagnosis, family screening, and treatment of inherited arrhythmogenic diseases in Europe: results of the European Heart Rhythm Association Survey. Europace. 2020; 22(12):1904–10. DOI: 10.1093/europace/euaa223
3. Gray B, Ackerman MJ, Semsarian C, et al Evaluation after sudden death in the young. A global approach. Circ Arrhythm Electrophysiol. 2019;12:e007453. DOI: 10.1161/CIRCEP.119.007453
4. Van den Heuvel LM, Do J, Yeates L, et al. Global approaches to cardiogenetic evaluation after sudden cardiac death in the young: A survey among health care professionals. Heart Rhythm. 2021;18(10):1637-44. DOI: 10.1016/j.hrthm.2021.03.037
5. Offerhaus JA, Bezzina CR, Wilde AAM. Epidemiology of inherited arrhythmias. Nat Rev Cardiol. 2020;17(4):205–15. DOI: 10.1038/s41569-019-0266-2
6. Peltenburg PJ, Crotti L, Roston TM, et al. Current gaps in knowledge in inherited arrhythmia syndromes. Neth Heart J. 2023;31(7-8):272–81. DOI: 10.1007/s12471-023-01797-w
7. Mariani MV, Pierucci N, Fanisio F, et al. Inherited arrhythmias in the pediatric population: an updated overview. Medicina 2024; 60:94. DOI: 10.3390/medicina600100
8. Schwartz PJ. 1970-2020: 50 years of research on the long QT syndrome: from almost zero knowledge to precision medicine. Eur Heart J. 2021;42(11):1063–72. DOI: 10.1093/eurheartj/ehaa769
9. Iskenderov B.G., Lokhina T.V., Molokova E.A. et al. Congenital long QT syndrome: genetic architecture, risk stratification and treatment approaches. International Journal of Heart and Vascular Diseases. 2024;12(42):5-15. Russian. DOI: 10.24412/2311-1623-2024-42-5-15
10. Piciacchia F, Auricchio A, Behr ER, et al. Family history of sudden cardiac death in the young and inherited arrhythmia syndromes: awareness and attitudes of general practitioners and private practice cardiologists. Circ Genom Precis Med. 2023; 16:92-3. DOI: 10.1161/CIRCGEN.122.003913
11. Wilde AAM, Semsarian C, Marquez MF, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. Heart Rhythm. 2022;19(7): e1-e59. DOI: 10.1016/j.hrthm.2022.03.1225
12. Kim JA, Chelu MG. Inherited arrhythmia syndromes. Tex Heart Inst J. 2021;48(4): e207482. DOI: 10.14503/THIJ-20-7482
13. Shlyakhto E.V., Arutyunov G.P., Belenkov Yu.N., Boytsov S.A. National guidelines for risk identification and prevention of sudden cardiac death. (2nd ed.). M.: Medpraktika-M, 2018. Russian.
14. Campuzano O, Sarquella-Brugada G, Cesar S, et al. Update on genetic basis of Brugada syndrome: monogenic, polygenic or oligogenic? Int J Mol Sci. 2020; 21(19):7155. DOI: 10.3390/ijms21197155.
15. Nakano Y, Shimizu W. Brugada Syndrome as a major cause of sudden cardiac death in Asians. JACC Asia. 2022;2(4):412-21. DOI: 10.1016/j.jacasi.2022.03.011
16. Krahn A, Laksman Z, Sy R, et al. Congenital long QT syndrome. JACC Clin Electrophysiol. 2022;8(5):687–706. DOI: 10.1016/j.jacep.2022.02.017
17. Wilde AAM, Amin AS, Postema PG. Diagnosis, management, and therapeutic strategies for congenital long QT syndrome. Heart. 2022; 108:332–38. DOI: 10.1136/heartjnl-2020-318259
18. Loginova E.N., Kirkh E.A., Nechaeva G.I. et al. Role of genetic research in the prevention of life-threatening rhythm and cardiac conduction disorders in young people. Russian Journal of Cardiology. 2022;27(10):4991. Russian. DOI: 10.15829/1560-4071-2022-4991
19. Waddell-Smith KE, Skinner JR, Bos JM. Pre-test probability and genes and variants of uncertain significance in familial long QT syndrome. Heart Lung Circ. 2020;29(4):512–19. DOI: 10.1016/j.hlc.2019.12.011
20. Vaykhanskaya TG, Sivitskaya LN, Persidskikh YuA, i dr. Long QT Syndrome: Clinical and Genetic Diagnostic Complications. Kardiologiya v Belarusi. 2020;12(5):747-66. Russian. DOI: 10.34883/PI.2020.12.5.012
21. Bockeria L.A., Pronicheva I.V., Serguladze S.Yu. Short QT syndrome and sudden cardiac death: recent clinical and genetic advances. Annaly aritmologii. 2022;19(3):196-206. Russian. DOI: 10.15275/annaritmol.2022.3.9
22. Dewi IP, Dharmadjati BB. Short QT syndrome: the current evidences of diagnosis and management. J Arrhythm. 2020; 36(6):962-6. DOI: 10.1002/joa3.12439
23. Dul'chenko V.S., Magomedova A. Kh., Vasilenko A.A., Khidirova L.D. Brugada syndrome. Eurasian heart journal. 2020; 1:130-5. Russian. DOI: 10.24411/2076-4766-2020-10004.
24. Priori SG, Marino M. Sudden cardiac death in the young: Are we still missing the opportunity to prevent recurrences in the family? Heart Rhythm. 2021;18(10):1645–46. DOI: 10.1016/j.hrthm.2021.06.1179
25. Shlobin NA, Thijs RD, Benditt DG, et al. Sudden death in epilepsy: the overlap between cardiac and neurological factors.

Brain Commun. 2024;6(5):fcae309. DOI: 10.1093/braincomms/fcae309

26. Vitali F, Brieda A, Balla C, et al. Standard ECG in Brugada syndrome as a marker of prognosis: from risk stratification to pathophysiological insights. Am Heart Assoc. 2021;10(10): e020767. DOI: 10.1161/JAHA.121.020767
27. Rieder M, Kreifels P, Stuplich J, et al. Genotype-specific ECG-based risk stratification approaches in patients with long QT syndrome. Front Cardiovasc Med. 2022;9:916036. DOI: 10.3389/fcvm.2022.916036
28. Kim CW, Aronow WS, Dutta T, et al. Catecholaminergic polymorphic ventricular tachycardia. Cardiol Rev. 2020; 28(6):325-31. DOI: 10.1097/CRD.0000000000000302
29. Pérez-Riera AR, Barbosa-Barros R, Samesina N, et al. Andersen-Tawil syndrome: a comprehensive review. Cardiol Rev. 2021; 29:165–77. DOI: 10.1097/CRD.0000000000000326
30. Voskoboinik A, Hsia H, Moss J, et al. The many faces of early repolarization syndrome: a single-center case series. Heart Rhythm. 2020;17(2):273-81. DOI: 10.1016/j.hrthm.2019.09.013
31. Tardo D, Peck M, Subbiah R, et al. The diagnostic role of T wave morphology biomarkers in congenital and acquired long QT syndrome: a systematic review. Ann Noninvasive Electrocardiol. 2023;28: e13015. DOI: 10.1111/anec.13015
32. Timothy A, Davies B, Laksman Z, et al. Provocation testing in congenital long QT syndrome: a practical guide. Heart Rhythm. 2023;20(11):1570–82. DOI: 10.1016/j.hrthm.2023.07.059
33. Tomassini L, Ricchezze G, Fedeli P, et al. New insights on molecular autopsy in sudden death: a systematic review. Diagnostics (Basel). 2024;14(11):1151. DOI: 10.3390/diagnostics14111151
34. Lahrouchi N, Raju H, Lodder EM, et al. Utility of post-mortem genetic testing in cases of sudden arrhythmic death syndrome. JACC. 2017;69:2134-45. DOI: 10.1016/j.jacc.2017.02.046