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Fundamentals of Pathophysiological Mechanisms of Brugada Syndrome and Analysis of Modern Strategies for Its Therapy

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Abstract

Sudden cardiac death is one of the leading causes of death with a high level of urbanization. Brugada syndrome is a genetically determined cardiac arrhythmia characterized by syncopal states, ST-segment rises (from point J) above the isoelectric line in the right precordial leads (V1–V3), which can disappear transiently, also inverted T wave, complete or incomplete blockage of the legs of the Gis beam, periodic elongation can be registered in these leads P–R interval with a high risk of life-threatening ventricular tachyarrhythmias (episodes of polymorphic ventricular tachycardia and ventricular fibrillation), usually developing in a dream or in a calm state. Often, patients also have supraventricular arrhythmias, more often atrial fibrillation. Over 15 years of studying pathology, data on acquired Brugada syndrome have accumulated. Changes in the ECG by the type of Brugada-like, without clinical confirmation of the syndrome, can be observed in patients with chest excavation, with hemopericardium. There are currently no convincing agreed data on the effectiveness of any medications in the long-term prevention of seizures, or they are contradictory. For patients with a high risk of sudden cardiac death, the method of therapy that increases life expectancy is the implantation of an electrocardio stimulator.

Disciplinary: Medicine.

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1 Introduction

Sudden cardiac death is one of the leading causes of death in developed and rapidly developing countries with a high level of urbanization. Sudden cardiac death accounts for almost 20% of all nonviolent deaths, especially among the young contingent of patients. Diseases associated with a high risk of this phenomenon include sudden infant death syndrome, prolonged Q–T interval syndrome, sudden unexplained death syndrome, arrhythmogenic right ventricular dysplasia, idiopathic ventricular fibrillation, and so on. One of the most mysterious diseases in this series is Brugada syndrome.

Although thousands of papers on this disease have been published all over the world, relevant thematic sections are regularly held at the largest international cardiological congresses, there are only isolated descriptions of this phenomenon in the Russian scientific literature at the time of 2021, which do not always fully reflect the typical picture of the disease. Despite this state of affairs, Brugada syndrome is, according to many experts, the cause of sudden non-coronary death at a young age in more than half of all cases.

2 Clinical characteristics of Brugada syndrome

Brugada syndrome is a genetically determined cardiac arrhythmia characterized by syncopal states, ST-segment rises (from point J) above the isoelectric line in the right precordial leads (V1–V3), which can disappear transiently. Also, inverted T wave, complete or incomplete blockage of the legs of the Gis bundle, periodic prolongation of the P–R interval with a high risk of life-threatening ventricular tachyarrhythmias (episodes of polymorphic ventricular tachycardia and ventricular fibrillation), usually developing in sleep or in a calm state, can be recorded in these leads. Often, patients also have supraventricular arrhythmias, more often atrial fibrillation [1].

In most cases, Brugada syndrome is observed in patients aged 30-40 years. For the first time, this syndrome, according to the official version, was described in a three-year-old girl who had frequent episodes of loss of consciousness and subsequently died suddenly, despite active antiarrhythmic therapy and implantation of a pacemaker. The clinical picture of the disease is characterized by the frequent occurrence of syncope against the background of attacks of ventricular tachycardia and sudden cardiac death, mainly in sleep, as well as the absence of signs of organic myocardial damage during autopsy [2].

The following clinical and electrocardiographic forms and variants of this syndrome are distinguished [3]:

- full form (typical ECG picture with syncope, presyncope, cases of clinical death, or sudden cardiac death due to polymorphic ventricular tachycardia);

– typical ECG picture in asymptomatic patients without a family history;

- typical ECG picture in asymptomatic patients, family members of patients with the full form of the syndrome;

– a typical ECG picture after pharmacological tests in asymptomatic subjects, family members of patients with the full form of the syndrome;

– a typical ECG picture after pharmacological tests in patients with repeated syncope or idiopathic atrial fibrillation;

- a typical ECG picture with an obvious block of a bundle of His, ST-segment elevation and prolongation of the P–R interval;

- a typical ECG picture with ST-segment elevation, but without prolongation of the P–R interval and block of a bundle of His;

– block of a bundle of His with moderate elevation of the ST segment;

– isolated prolongation of the P–R interval.

The severity of the clinical manifestations of the syndrome is determined by the degree of damage to the sodium channels. If less than 25% of the channels are damaged, the ECG pattern and rhythm disturbances are observed only after the introduction of sodium channel blockers. With an increase in the number of damaged sodium channels (over 25%), the risk of sudden cardiac death increases sharply [4,5].

Two types of ST-segment elevation in Brugada syndrome are described: "saddle" and "arch". The rise of the "arch" significantly prevails in symptomatic forms of Brugada syndrome, with *torsades de pointes* (TdP; pirouette ventricular tachycardia) in the anamnesis, while the "saddle" is more common in asymptomatic forms of the syndrome.

However, changes in the ECG may be transient, which requires the search for additional verification methods. Some authors suggest using high right thoracic leads for diagnosis. To verify the diagnosis, it is necessary to conduct stress tests with a drug load (class IA antiarrhythmic drugs), with the introduction of sodium channel blockers [6]. The test with sodium channel blockers is carried out in the conditions of the intensive care unit since during its implementation there is a high probability of developing ventricular tachycardia of the TdP type. It should be noted that polymorphic ventricular tachycardia is more associated with Brugada syndrome, whereas monomorphic ventricular tachycardia is less common and most common in children [7].

One of the less well-known, but the most informative predictors of a high risk of sudden cardiac death is the determination of the T-wave alternation during a physical exercise test or according to daily ECG monitoring [8]. The T–wave alternation is a numerical characteristic of changes in the morphology of the T-wave, manifested on an electrocardiogram in the form of alternating QRS complexes of various types. When performing tests with physical activity, the alternation of the T-wave is represented as a decrease in the amplitude or polarity of the T-waves and a change in the morphology of the ST segment in different complexes. The first studies of the diagnostic significance of T-wave alternation were conducted by D. Rosenbaum et al. The authors revealed a strong relationship between the magnitude of the T-wave alternation and the frequency of ventricular arrhythmias according to electrophysiological research. Based on the results of the work, it was concluded that the alternation of the T-wave serves as one of the markers of the occurrence of sudden cardiac death. Recent studies have proved the high informativeness of the T-wave alternation method for determining the group of patients who need an implantable

cardioverter-defibrillator.

Studies have shown that during the alternation of the T-wave, two mechanisms are triggered – the loss of the potential of the action of the epicardium and the latent 2nd phase of reentry [9]. The method of determining the alternation of the T wave helps to predict the risk of life-threatening ventricular arrhythmias and timely choose the right treatment tactics for patients with any pathology of the cardiovascular system.

In the literature, there are indications of the appearance of changes typical for Brugada syndrome on the ECG under the influence of other causes besides genetic pathology. Over 15 years of studying pathology, data on acquired Brugada syndrome have accumulated. Changes in the ECG by the type of Brugada-like, without clinical confirmation of the syndrome, can be observed in patients with chest excavation, with hemopericardium. There are reports of the appearance of signs of this syndrome with the use of large doses of cocaine, tricyclic antidepressants, hyperkalemia, hypercalcemia, thiamine deficiency, hyperparathyroidism, hypertestosteronemia, arrhythmogenic dysplasia of the right ventricle, pericarditis, myocardial infarction, Prinzmetal angina, pulmonary embolism, delaminating aortic aneurysm, various central and the autonomic nervous system, Duchenne muscular dystrophy, Frederick's ataxia [10-14].

Taking medications that inhibit sodium channels can also cause the development of the syndrome. Drug-induced Brugada syndrome has been described in the treatment of vagotonic drugs, beta-adrenergic agonists, beta-blockers, 1st generation antihistamines, antimalarial drugs, sedatives, anticonvulsants, neuroleptics, tri- and tetracyclic antidepressants, lithium preparations. According to in vitro and in vivo experiments, sectional and clinical studies, anticonvulsants, antidepressants, neuroleptics, anxiolytics, and normotimics are able to block fast potassium HERG channels, sodium channels (due to a defect in the SCN5A gene) and L-type calcium channels, thus causing functional insufficiency of all heart channels [15,16]. The reports available in the medical literature on a closely associated condition with the use of psychotropic drugs relate mainly to suicides, cases of overdose, and intoxication, that is, toxic doses of drugs [17-19]. At the same time, the registration of such brughad-like changes on the ECG accompanies the deterioration of the psychosomatic state of patients according to the type of "excessive tranquilization", with symptoms of general weakness, and drowsiness, hypotension, bradycardia, which resembles the clinical picture of deep hypersedation. After correction of therapy or withdrawal of a psychotropic drug, rapid reverse dynamics of ECG changes is observed following an improvement in the clinical condition of patients.

Accelerated inactivation of sodium channels caused by mutations of the SCN5A gene (associated with Brugada syndrome), as studies have shown, was accompanied by an increase in temperature. Indeed, several cases demonstrate that fever can contribute to the detection of a latent form of the disease [20].

3 Genetic Basis of Brugada Syndrome

To date, at least five genes responsible for the development of Brugada syndrome are known.

Mutation in any of them can lead to the development of the disease [21].

It is inherited by autosomal dominant type and is associated with mutations in the SCN5A gene located in the short arm of the 3rd chromosome 3p21-24 encoding the alpha-sodium channel subunit of cardiomyocytes. This gene encodes the protein structure of the α-subunit of the sodium channels that provide the sodium current of the action potential. Mutations in this gene can also lead to Q–T elongation syndrome and cardiac conduction disorders. This mutation is considered to be the primary "electrical" heart disease developing due to abnormal electrophysiological activity of the epicardium of the right ventricle in the area of the outflow tract. A certain number of mutations of this gene can cause a number of syndromes that overlap with each other. About 10 years ago, C. Antzelevitch et al. Two new genes have been discovered that cause ST-segment elevation and shortening of the Q–T interval, which leads to a combination of Brugada syndrome with short Q–T interval syndrome [22].

4 Transmural Cellular and Ionic Changes

For normal coupling between excitation and contraction, as well as for maintaining the heart rate, coordinated activity of the ion channels of the heart muscle is necessary. Ankyrins are intracellular polypeptides necessary for the biosynthesis and maintenance of membrane domains in excitable and non–excitable cells. They are membrane adaptive molecules that play an important role in the interaction of integral membrane proteins and the cytoskeleton spectrin network. The ankyrin polypeptide family is involved in the distribution, fixation, and stabilization of membrane proteins. Mutation of ankyrin genes leads to such a severe hereditary disease as a fatal arrhythmic syndrome. At the same time, there are two ankyrin products, also known as ankyrin-B and ankyrin-G, associated with the distribution-attachment of various membrane ion channels and carriers to the excited membrane domains of cardiomyocytes [1,13].

Ankyrin-B and ankyrin-G are components of the heart muscle that attach various ion channels, pumps, and carriers to physiological sites of exposure. Ankyrin-B mutations are known to cause cardiac arrhythmic syndrome associated with a violation of calcium homeostasis, and ankyrin-G is associated with the main potential-dependent cardiac sodium channels, and the loss of this interaction due to mutations leads to Brugada syndrome. According to the results of studies of neurons and cardiomyocytes, ankyrin-G participates in the general mechanism of localization of potential-dependent Na(v) channels in the places of functioning of various excitable cells. Ankyrin-G is necessary for the expression of cardiac potential-dependent Na channels in specialized domains of cardiac cell membranes, its mutation leads to a loss of Na distribution on the cell surface of cardiomyocytes. Changes in the SCN5A gene that blocks interaction with ankyrin-G lead to impaired membrane expression. And in the final – Brugada syndrome [13].

5 Therapy of Brugada Syndrome

Treatment of Brugada syndrome is carried out by taking into account the clinical features of the disease, and the nature of genetic disorders (the presence of defective Na-channel protein). In the presence of clinical symptoms, patients need implantation of a cardioverter-defibrillator. For

antiarrhythmic drugs, it is necessary to prescribe class IA drugs (quinidine and disopyramide) or amiodarone. It is necessary to avoid prescribing class I drugs, such as novocainamide, and flecainide, which, by blocking the sodium current in isolation, provoke the manifestation of the syndrome. Drugs of class IC, such as flecainide and propafenone, and class IA, such as procainamide, are contraindicated because they contribute to the detection of latent Brugada syndrome and cause arrhythmogenesis. There are isolated indications of the effectiveness of preventing ventricular arrhythmias when prescribing propranolol and disopyramide, although they can lead to an even more pronounced rise in the ST segment. Disopyramide in some cases normalizes the elevation of the ST segment, and in some also reveals a latent syndrome [24]. There is an observation indicating the prevention of recurrence of ventricular fibrillation with intravenous administration of isoproterenol.

Currently, the search is underway for other drugs that could be used to treat this syndrome. For example, a case of preventing regular episodes of ventricular fibrillation with oral administration of cilostazol is described. Catecholamines, beta-adrenomimetics, and alpha-blockers reduce the rise of the ST segment. The presence of pronounced Ito is a component of the mechanism of development of the syndrome. Therefore, the best approach is to inhibit Ito [25]. It is known that quinidine in a low dose (300-600 mg) can prevent electrophysiological induction of ventricular tachycardia [26].

Another drug considered for these purposes is tedisamil, which is currently used to treat atrial fibrillation. Tedisamil may be more effective than quinidine. Tedisamil and quinidine are able to suppress the mechanism of development of the syndrome by blocking Ito. But at the same time, they block specific channels, which contribute to the occurrence of the Q–T interval prolongation syndrome. Thus, these agents can replace the occurrence of one form of polymorphic ventricular tachycardia with another, especially in bradycardia and hypokalemia. However, most patients with Brugada syndrome are healthy men for whom the risk of drug-induced TdP is low. The beta-adrenergic drug isoproterenol is also effective, which increases the flow of calcium [27, 28].

In some cases, the use of isoproterenol in combination with quinidine normalizes the elevation of the ST segment, especially in children. A new drug is phosphodiesterase (a cilostazol inhibitor), which normalizes the ST segment by increasing calcium flow and reducing Ito.

6 Conclusion

The only reliably effective method of treating patients with the symptomatic variant of Brugada syndrome is currently considered to be the implantation of an electrocardio-stimulator, which prevents episodes of sudden cardiac death [28-30]. Among the indications for implantation of an electrocardio-stimulator in asymptomatic patients are currently considered: male sex, age 30-40 years, family history of cardiology, the presence of a mutation in the SCN5A gene, the presence of spontaneous changes in the V1– V3 leads on the ECG [41].

Genetically determined damage to sodium channels theoretically implies lower effectiveness of group 1 drugs, as well as the possibility of an arrhythmogenic effect when using them. According

to the algorithm for the formation of antiarrhythmic therapy, known as the "Sicilian Gambit", antiarrhythmic drugs that provide active blockade of sodium channels are novocainamide, disopyramide, quinidine, ritmonorm, giluritmal, flecainide, encainide. A less pronounced blocking effect was observed in lidocaine, mexiletine, tocainide, bepridil, verapamil, Cordarone, and obsidian. It can be assumed that with Brugada syndrome, it is safer to use drugs that do not block sodium channels – diltiazem, bretylium, so tales, Corgard. There is currently no convincing consistent data on the effectiveness of any medications in the long-term prevention of seizures or contradictory. For patients with a high risk of sudden cardiac death, the method of therapy that increases life expectancy is the implantation of an electrocardiostimulator.

7 Availability of Data And Material

Data can be made available by contacting the corresponding author.

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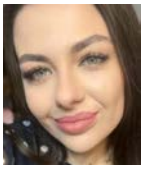

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