Malignant arrhythmia with Variants of Desmocollin-2 and Desmplakin Genes
A Case Report

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Summary
Malignant arrhythmia is a fast cardiac arrhythmia that can lead to a hemodynamic abnormality within a short time, most of which is ventricular tachycardia or ventricular fibrillation (VF), which should be managed in time. Both organic and nonorganic cardiac diseases have the potential to cause malignant arrhythmia. We report a noteworthy case of malignant arrhythmia in a teenager during exercise. Transthoracic echocardiography, cardiac magnetic resonance (CMR), electrophysiological study, magnetic resonance imaging of the brain, electroencephalography, chest X-ray, and blood tests were all normal. Twelve-lead electrocardiography showed incomplete right bundle branch block (IRBBB). Two heterozygous missense variants of the desmocollin-2 gene (DSC2, c.G2446A/p.V816M) and desmplakin gene (DSP, c.G3620A/p.R1207K) were detected in the peripheral blood of this teenager and his father by genetic testing, which encoded a desmosomal protein that was related to arrhythmogenic right ventricular cardiomyopathy (ARVC). In these two rare variants, DSC2 V816M has been reported but uncertain significance, whereas DSP R1207K is never reported. Therefore, the two site variants in DSC2 and DSP genes are likely to become a new research focus for diagnosis and treatment of ARVC in the future. Meanwhile, this report emphasizes that, in addition to a standard set of laboratory tests and examinations, genetic testing may be useful for analyzing the causes of malignant arrhythmia.

Key words: Genetic testing, Arrhythmogenic right ventricular cardiomyopathy

Malignant arrhythmia is a fast cardiac arrhythmia that can lead to a hemodynamic abnormality within a short time, most of which is ventricular tachycardia or VF, which should be managed in time. A significant number of cases of malignant arrhythmia, especially in teenagers, are caused by inherited ventricular arrhythmias. Ventricular arrhythmias with genetic components can be classified into two subgroups: primary electrical diseases or channelopathies, which usually have no overt structural cardiac disease and secondary arrhythmogenic cardiomyopathies.1)

Genetic variation in myocardial ion channels leads to abnormal ventricular depolarization and repolarization, and to ventricular arrhythmia. This type of disease is known as cardiac ion-channel disease and includes Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), long-QT syndrome, and short-QT syndrome. The cardiac structure of these diseases is usually normal. Malignant arrhythmia caused by structural cardiac disease includes the inherited cardiomyopathies, such as ARVC, dilated cardiomyopathy, and hypertrophic and restrictive cardiomyopathies. Other structural causes of malignant arrhythmia in teenagers include myocarditis and congenital heart diseases.

Many studies have shown that the characteristic inherited pattern of these diseases is an autosomal-dominant trait with incomplete expression, as well as at least five primary genes (DSC2, DSP, Plakophilin 2, Desmoglein 2, and Junction plakoglobin), which encode proteins of the cell-cell junctions at the intercalated disc that play an essential role in ARVC.2-4) ARVC is an uncommon cardiac disease characterized by myocyte loss and fibro-fatty tissue replacement, resulting in life-threatening ventricular arrhythmias, gradual ventricular dysfunction of the right and the left ventricles, and ultimately heart failure.5) Here, we report heterozygous missense variants (c.2446G>A/p.V816M) in exon 18 of DSC2 (location:18p12.1) and (c.3620G>A/p.R1207K) in exon 24 of DSP (location:6p24.3), which may lead to the occurrence of malignant arrhythmia.

Case Report
A 13-year-old teenager collapsed suddenly while tak-
ing morning exercises. There were no convulsions, froth at the mouth, and facial cyanosis. At school, teachers performed cardiopulmonary resuscitation before a physician reached the scene after 15 minutes. VF was recorded in the ambulance, and multiple defibrillations were performed. Spontaneous rhythm and circulation were recovered with the use of advanced basic life support. Next, the teenager was admitted to the intensive care unit for further treatment and monitoring, and he recovered completely a few days later.

Family history revealed the sudden unexplained death of his uncle at the age of 25. No history of heart and respiratory diseases were found in the current patient. Electrocardiography (ECG) showed IRBBB after a successful rescue (Figure 1). Two days after admission, ECG was normal. During the hospital stay, no malignant arrhythmia was detected by Holter monitoring. Routine blood tests, liver and renal function tests, and serum electrolytes were all normal. Transthoracic echocardiography, CMR, electrophysiological study, and chest X-ray were normal. Cox-sackievirus and respiratory syncytial virus infections were excluded by the absence of viral nucleic acids. Whole exome and Sanger sequencing were performed using peripheral blood by the Beijing Medical Technology Co. Ltd. Testing Center. Genes that predispose to cardiomyopathy and arrhythmia were screened for potential pathogenic mutations. The patient carried variants of DSC2 (c.G2446A/p.V816M) (Figure 2A) and DSP (c.G3620A/p.R1207K) (Figure 2B). Significantly, genetic testing found that his father also carried variants of DSC2 (c.G2446A/p.V816M) and DSP (c.G3620A/p.R1207K) (Figure 2C). No symptoms of chest distress, palpitations and fainting were found, and ECG and transthoracic echocardiography was normal in his father. His mother’s genetic testing was normal (Figure 2E and F). We constructed a pedigree family verification table (Table I). Pedigree of the family of three generations showed that two members carried variants of DSC2 (c.G2446A/p.V816M) and DSP (c.G3620A/p.R1207K) (Figure 3). In accordance with the American and European guidelines,6) we proposed treatment with an implantable cardioverter defibrillator (ICD). For various reasons, however, treatment was refused by his parents. We advised that avoidance of competitive sports be recommended for the patient. Generally, restricting physical activity and exercise were important because ICD was not implanted.

**Discussion**

Malignant arrhythmia can cause hemodynamic abnormality within a short time, resulting in syncope and even sudden death. Genetic variations that cause myocardial ion-channel and arrhythmogenic cardiomyopathies in teenagers are major causes of malignant arrhythmias. According to the patient’s history and related examinations, BrS and ARVC are considered to be the most likely cause of malignant arrhythmia in the present case.

BrS was initially described by Pedro and Joseph Brugada in 1992.7) BrS is linked to ventricular arrhythmia7) and is estimated to cause 4% of all sudden cardiac deaths (SCDs). The majority of patients with BrS are diagnosed only after cardiac arrest.8) It is hard to evaluate the true prevalence of BrS because it is usually hidden, and the classical ECG pattern can be transient.9) BrS is a nonstructural cardiac condition, which is a significant cause of sudden death in young adults (< 40 years) and more
prevalent in Asia. At present, the diagnosis of BrS is based on patients’ clinical symptoms and the characteristic ECG pattern. Yagi, et al. found that low serum levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are risk factors for VF in patients with BrS. Therefore, the detections of EPA and DHA are positive signs in preventing VF in patients with BrS. In patients with BrS, VF primarily occurs between midnight and early morning. Eighty percent of patients with recorded VF have a history of syncope. In some patients, genetic testing can detect specific mutations in genes such as SCN5A. Those who were saved from SCD have a higher risk of recurrent VF. It is reported that about 15% of cases of ARVC overlap with BrS. In the present case report, ECG only showed IRBBB. Brugada can be intermittent, so it cannot be ruled out that the cause of malignant arrhythmia in the present case was BrS. The patient should be followed up closely after discharge.

ARVC is a progressive inherited cardiomyopathy. Prior studies have proved that genetic defects can be validated in ~40% of cases. According to clinical research,
the prevalence of ARVC is estimated from 1:2000 to 1:5000 in the general population. ARVC can be divided into four phases: early hidden phase, overt electrical disorder phase, right ventricular failure phase, and biventricular failure phase. The early hidden phase may lead to mild ventricular arrhythmia. Patients are often asymptomatic but at risk of SCD, especially during strenuous exercise. In the overt electrical disorder phase, there is evident ventricular arrhythmia and more obvious abnormalities of right ventricular morphology and function. In the right ventricular failure phase, there is further disease progression, but the left ventricular function is relatively normal. In the biventricular failure phase, advanced disease develops into biventricular failure, leading to a phenotype similar to dilated cardiomyopathy. Current diagnostic methods for ARVC include ECG, electrophysiological examination, transthoracic echocardiography, CMR, endomyocardial biopsy, and genetic testing. For this patient, although the examination of transthoracic echocardiography and CMR did not find structural and functional anomalies, genetic testing supports ARVC. We suspect that in the early phase of the disease, in very few cases, fibrous adipose tissue replaces the myocardial tissue, so transthoracic echocardiography and CMR cannot detect any changes in cardiac structure and function. His father’s ECG and transthoracic echocardiography are normal. It is regrettable that CMR inspection intended for his father is refused by his father.

So far, ~84 site mutations of DSC2 and ~148 site mutations of DSP have been reported in ARVC. DSP p.R1207K was the first reported and was detected in the present case of exercise-induced malignant arrhythmia in a teenager. At the same time, we confirmed that the heterozygous missense variants carried by this patient were inherited from his father. The cause of death of his uncle could have been related to DSC2 and DSP heterozygous missense variants. DSC2 p.V816M and DSP p.R1207K could be involved in the pathogenesis of ARVC. According to the Modification of ARVC Task Force criteria, this patient only met one major diagnostic criterion and one secondary diagnostic criterion, so the diagnosis of ARVC remained undefined. ICD implantation should be considered for especially high-risk individuals, whether they have BrS or ARVC. In China, however, numerous patients refuse to receive ICD implantation on account of poverty. Welfare policy and medical insurance should take into account these conditions of low morbidity but high mortality. Genetic testing is of great value in the diagnosis of BrS, ARVC, and CPVT. Nevertheless, genetic testing in China has not been extensively used for the following two reasons: (1) technical aspects and the cost of laboratory examination restrict the use of genetic testing in some disadvantaged areas; and (2) some doctors do not abide by the latest guidelines. Hence, genetic testing should receive adequate attention in the diagnosis of malignant arrhythmia.

In summary, we report a rare case with two heterozygous missense variants in DSC2 (c.G2446A/p.V816M) and DSP (c.G3620A/p.R1207K) that affected a desmosomal protein that was related to ARVC. Two site variants in DSC2 and DSP genes are likely to become a new research focus for diagnosis and therapy of ARVC in the future. Therefore, our next program will be for DSC2 (c.G2446A/p.V816M) and DSP (c.G3620A/p.R1207K) for some further functional analysis. This report emphasizes that, in addition to a standard set of laboratory tests and examinations in the hospital, genetic testing may be useful for analyzing the causes of malignant arrhythmia.

Disclosures

Conflicts of interest: The authors declare that they have no conflicts of interest.

Informed consent: Consent was obtained from relatives of the patient for publication of this report and any accompanying images.

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