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CASE REPORT

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Three cases of catecholaminergic polymorphic ventricular tachycardia with prolonged QT intervals including two cases of compound mutations

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Abstract

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is one of the leading causes of sudden arrhythmic death in the young. The QT interval in CPVT patients is typically within the normal range. However, those with prolonged QT interval have often been diagnosed with mutation-negative long QT syndrome (LQTS). We report three CPVT patients with prolonged QT interval. Case 1 and 2 were diagnosed as LQTS at first. Genetic test using next-generation sequencing (NGS) revealed *RyR2* mutations. We should consider genetic test using NGS to identify the genes responsible for CPVT in mutation-negative LQTS.

KEYWORDS
catecholaminergic polymorphic ventricular tachycardia, long QT syndrome, next-generation sequencing, *RyR2*, sudden arrhythmic death

1 | INTRODUCTION

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmic disorder characterized by bidirectional or polymorphic ventricular tachycardia induced by exercise or emotional stress.[1] The incidence of CPVT is reported to be as high as 1:10 000, but its actual prevalence is unclear.[2]

The symptoms of CPVT with QT prolongation and long QT syndrome (LQTS), especially in LQTS type 1, are similar in that exercise can induce ventricular arrhythmia, which may result in sudden cardiac death. An accurate diagnosis is essential because the arrhythmic event rate with β-blockers remains significantly higher in patients with CPVT than in those with LQTS.[1] Exercise stimulates the sympathetic nerves and promotes the secretion of catecholamines. CPVT patients develop arrhythmia because of the large quantities of Ca^{2+} that are released from the sarcoplasmic reticulum, while LQTS1 patients develop torsades de pointes through increased early afterdepolarization and higher heterogeneity in monophasic action potential duration among different sites in the ventricular muscles.

2 | CASE REPORT

2.1 | Case 1

The patient was a 9-year-old female with no significant medical history but who had a family history of cardiac events (Figure S1A).

She experienced a witnessed sudden cardiac arrest while running. She was transferred to the emergency hospital. QT prolongation was seen under mild hypothermia on the next day (Figure 1A),[3] and propranolol was started. On presentation at our hospital 18 days after the event, she showed both QT prolongation (Figure 1B) and bigeminy of ventricular premature contractions on Holter electrocardiography (ECG). She was diagnosed as LQTS, and propranolol was continued. Conventional genetic testing results revealed no pathogenic mutations in LQTS-related genes (Data S1). Two years after, Genetic testing using next-generation sequencing (NGS) (Table S1) revealed a *RYR2* mutation (Figure S1B).

2.2 | Case 2

A 29-year-old female was referred to our hospital for genetic analysis. At the age of 14 years, she experienced cardiac arrest while running. Her initial diagnosis was LQTS based on a prolonged QT interval, and propranolol was started. Four months after the event, her 15-year-old brother died suddenly while watching television (Figure S2A). She showed QT prolongation on Holter ECG (Figure 1C). Conventional genetic testing failed to identify pathogenic mutations in LQTS-related genes. At 36 years of age, genetic testing using NGS showed compound *RYR2* mutations (Figure S2B).

2.3 | Case 3

A 16-year-old male was referred to our hospital because of two syncopal episodes while running. He had no family history of sudden death (Figure S3A). Holter ECG showed prolonged QT interval and bidirectional VT (Figure 1D,E). Bidirectional VT completely disappeared on Holter ECG after combination therapy of carvedilol and flecainide. Genetic testing using NGS revealed compound *RYR2* mutations (Figure S3B).

No family members in any of our three cases agreed to genetic testing.

The pathogenesis of each mutation was evaluated by PolyPhen2, SIFT, and CADD, and none of the mutations were predicted to be benign (Table S2).

3 | DISCUSSION

In our study, QT prolongation was present on the Holter ECGs in all cases. The standard of QT intervals on Holter ECG is not clear; however, Page et al[4] showed that Holter ECG was useful in patients with LQTS to identify dynamic changes in QTc intervals.

Several subtypes of CPVT have been reported. The most common subtype is caused by mutations in *RyR2* (CPVT1). This accounts for more than 50% of CPVT cases. The inheritance of CPVT1 is autosomal dominant, and sudden death was observed in about 10% of patients. The second most common subtype of CPVT is caused by a *CASQ2* anomaly (CPVT2). This accounts for 1% of CPVT cases and is inherited in an autosomal recessive manner.

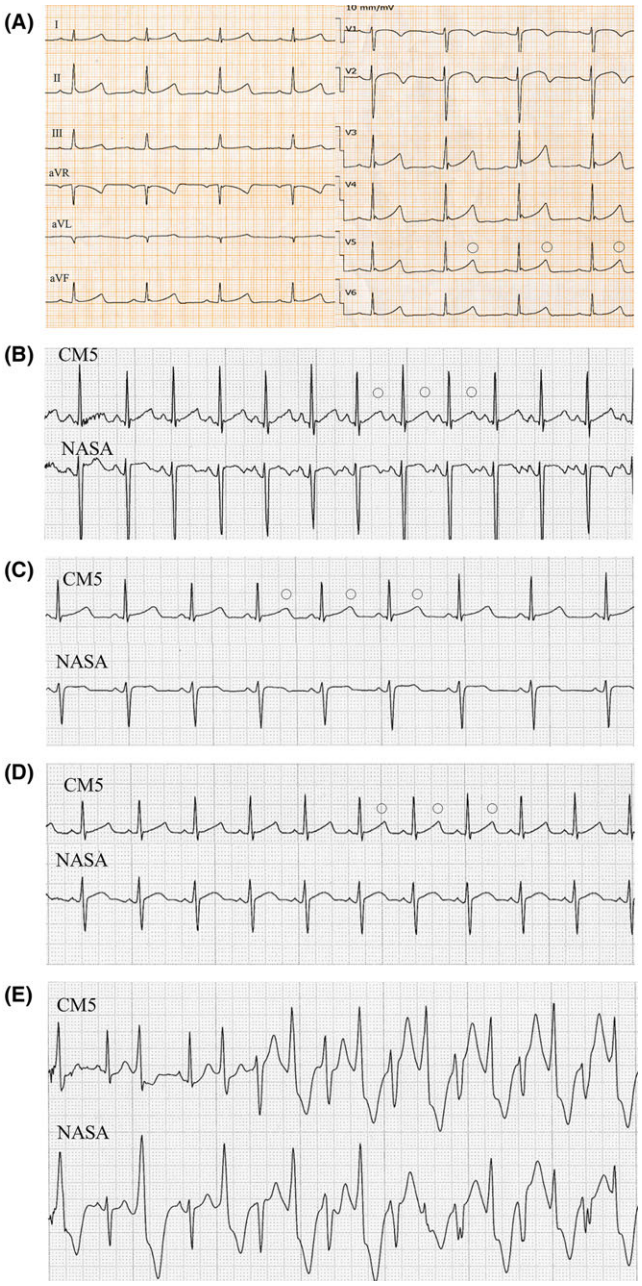

FIGURE 1 ECGs in case 1-3. A, Resting ECG the day after aborted cardiac arrest showing QT prolongation (the mean QTc values of three consecutive beats; QTc by Bazett's formula (QTcB), $0.488^{1/2}$; QTc by Fridericia's formula (QTcF), $0.492^{1/3}$); marked (○) QT intervals and precedent RR intervals were measured. Calibration of the limb leads is 1 mV = 10 mm (case 1). B, C, D, Holter ECGs showing prolonged QT interval in case 1 (QTcB, $0.506^{1/2}$; QTcF, $0.452^{1/3}$), in case 2 (QTcB, $0.522^{1/2}$; QTcF, $0.500^{1/3}$), and in case 3 (QTcB, $0.497^{1/2}$; QTcF, $0.463^{1/3}$); marked (○) QT intervals and precedent RR intervals were measured, respectively. E, Holter ECG showing bidirectional ventricular tachycardia (case 3)

Case 3 was treated with flecainide in addition to carvedilol because a diagnosis of CPVT by typical ECG increases the likelihood of being positive for *RyR2* mutations. Drug therapies included the medicines carvedilol and flecainide. In terms of nondrug therapies,

implantable cardioverter defibrillation is the recommended option for adults with a history of VT to prevent sudden death in CPVT. Left cardiac sympathetic denervation and catheter ablation are alternative options whose efficacy has been reported in some studies.

The exact reasons for prolonged QT interval in patients with *RYR2* mutations are not clearly known. Makita et al[5] reported that two of five cases with mutations in calmodulin had overlapping features of CPVT and LQTS. They speculated that abnormal calmodulin regulation of L-type Ca^{2+} channels would account for impaired myocardial repolarization similar to Timothy syndrome, whereas dysregulation of *RYR2* would lead to altered regulation of intracellular Ca^{2+} homeostasis as expected in CPVT. Future studies are needed to clarify the reasons for prolonged QT interval in patients with *RYR2* mutations. The N-terminus of RyR2 contains a binding site that is important to the protein's function (Figure S4). Accordingly, mutations in this region are more likely to result in visible functional impairments, which we suggest explains the apparent bias toward N-terminal mutations.

The implication of our findings is that NGS approaches may be preferable for patients or their family members with syncope, aborted cardiac arrest, or sudden death.

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CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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