A delayed diagnosis of catecholaminergic polymorphic ventricular tachycardia with a mutant of RYR2 at c.7580T>G for 6 years in a 9-year-old child

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Abstract

Rationale: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare but potentially lethal inherited arrhythmia syndrome induced by adrenergic stress. Due to the atypical clinical manifestations in early age, limited recognition and experience of pediatric cardiologists, and low awareness of the significance of genetic diagnosis in some underdeveloped areas in China, a delayed or missed diagnosis of CPVT in children is common and concerning.

Patient concerns: A 9-year and 3-month male child with recurrent exercise-induced syncope accompanied by convulsion was initially misdiagnosed as epilepsy since the first manifestation at the age of 3 years. Due to the identification of polymorphic ventricular premature beats, nonsustained ventricular tachycardia (VT), and supraventricular tachycardia, a cardiogenic etiology was established. The patient received a successive treatment by propafenone, amiodarone, a combination of amiodarone with metoprolol, and metoprolol alone for up to 6 years.

Diagnoses: Given the poor response to conventional antiarrhythmics, excise-induced syncope, QRS morphology and a structurally normal heart, the diagnosis of CPVT was suspected, and ultimately confirmed by detection of polymorphic and bidirectional VT with degeneration into ventricular fibrillation during exercise testing. In addition, a heterozygous mutant of RYR2 at c.7580T>G was identified by genetic testing.

Interventions: Due to the unavailability of flecainide in China and the refusal of implantable cardioverter defibrillator implantation by his parents, this patient continued to be treated with oral metoprolol.

Outcomes: Unfortunately, the effect was unfavorable during 4 months outpatient follow-up.

Lessons: CPVT should be suspected in young patients with a normal baseline electrocardiogram (EKG), a structurally normal heart and polymorphic and/or bidirectional ventricular tachycardia induced by exercise or emotional stress. Exercise and genetic testing is essential and significant for a timely and accurate diagnosis of CPVT. The current study firstly reported a case with CPVT associated with a mutant of RYR2 at c.7580T>G in children.

Abbreviations: ARVD = arrhythmogenic right ventricular dysplasia, BP = blood pressure, CPVT = catecholaminergic polymorphic ventricular tachycardia, CT = computed tomography, EKG = electrocardiogram, HR = heart rate, ICD = implantable cardioverter defibrillator, MRI = magnetic resonance imaging, QTc = corrected QT interval, RSD = renal sympathetic denervation, RSN = renal sympathetic nerve, SCD = sudden cardiac death, SVT = supraventricular tachycardia, VPB = ventricular premature beat, VT = ventricular tachycardia.

Keywords: catecholaminergic polymorphic ventricular tachycardia, children, delayed diagnosis, RYR2
1. Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia syndrome characterized by syncope and cardiac arrest occurring in children and young adults with morphologically normal hearts and normal baseline electrocardiograms (EKGs). Cardiac events are induced by sympathetic activation and physiological release of catecholamine during physical or emotional stress.[1] The hallmark sign of CPVT manifests as ectopic beats, bigeminy, and polymorphic or bidirectional ventricular tachycardia (VT).[1] Patients with CPVT typically present to medical attention most frequently during childhood or early adolescence, and the mean age at first symptom is 10 years.[1,2] It belongs to a group of inheritable disorders termed as “channelopathies,” caused by gene mutations encoding channel-proteins responsible for calcium homeostasis in cardiomyocytes.[3] Two main genetic variants have been identified as causative factors for CPVT: RyR2, encoding the cardiac ryanodine receptor; CASQ2, encoding cardiac calsequestrin.[2,3] Therefore, genetic testing is always quite essential and important to unveil the diagnosis for those cases with a clinical suspicion of CPVT, such as syncope occurring during exercise or the young children with genotype-positive family histories.

Although it is a rare disease, with a prevalence estimated at 1:10,000 in population, early and prompt recognition of CPVT is clinically substantial due to its high mortality rate of up to 50% in severely affected untreated patients by the age of 20 years.[1] However, it is always difficult to establish a timely and accurate diagnosis due to a normal cardiac imaging, unremarkable baseline EKG, and commonly misattributed syncope episodes, thus leaving the patients untreated and exposed to arrhythmic risk. Children with CPVT are usually more severely affected than adults. The clinical presentations of affected individuals with younger age are more atypical in comparison with the older ones, some of whom even experience sudden unexpected death.[4] In addition, due to the limited recognition and experience of pediatric cardiologists and low awareness of the significance of genetic testing in the accurate diagnosis of CPVT in some underdeveloped areas in China, a delayed or missed diagnosis of CPVT in children is always more common and concerning. Here we reported 1 substantially delayed diagnosis of CPVT with RYR2 7850T>G mutant for up to 6 years since the symptom onset at the young age of 3 years old, aiming to share some experience and improve the recognition of CPVT for the pediatric cardiologists, particularly in developing countries.

2. Case report

The case was a 9-year and 3-month male child, who experienced recurrent episodes of syncope accompanied by convulsion, was misdiagnosed as epilepsy since the first manifestation at the age of 3 years. Exercise-induced syncope followed by generalized tonic-clonic spasms had been noted since symptom onset. However, there was no positive family history of sudden cardiac death (SCD), seizure, pregnancy loss, and neonatal death. He was admitted to our pediatric cardiovascular department for the first time because of being unresponsive to 3 months of the antiepileptic treatment (sodium valproate, 20 mg/kg per day). On arrival, he was clear, afebrile, no tachycardia, no tachypnea, no hypotension (blood pressure: 90/47 mm Hg), and no hypoxia (SpO2: 97%). The vital signs were stable, and no positive findings were identified by physical examination.

Blood routine, blood electrolytes, blood glucose, blood gas analysis, myocardial troponin, autoantibody, antistreptolysin O, acute phase protein, and thyroid function were unremarkable. Liver function test and creatinine level were also normal. Computed tomography and magnetic resonance imaging (MRI) of brain without enhancement did not reveal any intracranial hemorrhages, ischemic changes, or space-occupying lesions. Electroencephalogram detected no epileptiform discharge. Chest X-rays showed a mildly increased cardiothoracic ratio (0.53). The echocardiography detected mild mitral and tricuspid valve regurgitation without other remarkable findings. A 12-lead EKG showed sinus bradycardia (heart rate [HR]: 45 bpm), normal atrioventricular and intraventricular conduction and normal QT interval (corrected QT interval [QTc]: 435 ms). Repeated 24-h Holter monitoring demonstrated polymorphic ventricular premature beats (VPBs) (bigeminy and trigeminy), nonsustained VT, and supraventricular tachycardia (SVT). Regrettably, due to the lack of knowledge about CPVT, exercise stress testing was not undergone to further explore the underlying etiology resulting in arrhythmia. Oral administration of propafenone (15 mg/kg per day) was initiated, and the patient was discharged, taking periodic outpatient follow-up. However, it was proved to be noneffective after more than 2 years of follow-up. At the age of 5 years and 11 months, he was hospitalized again in our department because of more severe episodes of exercise-induced syncope and convulsion. At this time, sinus bradycardia (58 bpm), polymorphic VTs, and VPBs (trigeminy and bigeminy) on EKGs became more prominent. For the echocardiography, mildly dilated left ventricle with normal systolic function was noted. Thus, propafenone was discontinued, and oral amiodarone (loading dose: 15 mg/kg per day; maintenance dose: 5 mg/kg per day) was prescribed. Yet he was refractory to the amiodarone therapy, and experienced recurrent arrhythmic events at exercise or emotional stress during outpatient follow-up. Based on phases of QT interval prolongation (QTc 460–475 ms) observed on Holter monitoring, dose of amiodarone was gradually tapered. At the third admission, the patient received a combination of amiodarone (3 mg/kg per day) with metoprolol (initial dose: 0.4 mg/kg per day; maximal dose: 2 mg/kg per day), and subsequently metoprolol alone due to phases of QT prolongation. However, the effects seemed discouraging as well. On account of the excise-induced syncope, QRS morphology, a structurally normal heart, poor response to conventional antiarrhythmics (propafenone, amiodarone, and metoprolol) (Fig. 1) and a review of the literature, an increased clinical suspicion of CPVT was initiated, and exercise testing was performed. Encouragingly, on exercise testing, polymorphic VPB (bigeminy and couplets), polymorphic and bidirectional VT with degeneration into ventricular fibrillation were detected during exercise (Fig. 2). In light of the above findings, a clinical diagnosis of CPVT was established.

Based on the sequencing analysis, a heterozygous mutant of RYR2 at c.7580T>G had been identified, where nucleotide 7580 changed from T (Thymine) to G (Guanine) in exon 50, while his parents and sibling were wild types (Fig. 3). As RYR2 mutant might also be associated with arrhythmogenic right ventricular dysplasia (ARVD), we reviewed the clinical manifestations and related examinations (such as cardiac MRI) and excluded the possibility of ARVD. Because mutation of RYR2 gene was the most frequent variant of CPVT, the diagnosis was ultimately confirmed genetically up to 6 years later since the symptom onset at the young age of 3 years old.

According to 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD, this patient continued to be treated with oral metoprolol (maximal tolerated dose: 3 mg/kg per day). Unfortunately, the
effect was unfavorable during 4 months follow-up (Fig. 1). As the recommended flecainide is unavailable in our country, implantable cardioverter defibrillator (ICD) therapy was suggested. Nevertheless, his parents refused to have an ICD implantation due to the economic factor and the possible related complications. This patient continued to be treated with oral metoprolol and followed up in our outpatient department.

3. Discussion

CPVT is one of the most lethal cardiac channelopathies, which mainly occurs during children or early adolescents. However, the recognition and diagnosis are clinically challenging attributed to normal resting EKGs, and a structurally normal heart. Since CPVT-related syncope might be associated with convulsion, children are likely to be initially misdiagnosed as a non-cardiogenic entity (such as epilepsy), especially for the patients younger than 8 years, which is in consistence with the condition of the case reported in the present study. In this case, the presenting symptom was attributed to arrhythmic conditions according to the positive findings on Holter recording during the first admission, when antiepileptic drug was found to be ineffective. Notably, in spite of the arrhythmia refractory to conventional therapy, it took such a long time to gain enough clinical suspicion of CPVT and then specific tests were performed. The difficulty to recognize CPVT patients was reported by Roston et al, who found in a study on 226 CPVT patients that the establishment of diagnosis was approximately 2 years after the first symptomatic episode. In addition, more than 60% of patients received a missed diagnosis at the initial evaluation.

According to current guidelines, the clinical diagnosis of CPVT is based on the documented polymorphic VT induced by
adrenergic stimuli, that is, emotions or exercise, in patients in absence of any other structural or electrical cardiac abnormality. The bidirectional VT (characterized by a 180° beat-to-beat rotation of the ectopic QRS complexes) detected at exercise testing is another highly specific sign of CPVT. Despite the often unremarkable baseline EKGs present in CPVT patients, some features, such as sinus bradycardia, SVT, and phases of QT prolongation, detected in the present case, may help the pediatricians to identify affected individuals. First, most CPVT patients demonstrate a prominent sinus bradycardia in resting EKG, which may be a consequence of the diastolic calcium leakage from the ryanodine receptor, resulted from either RyR2 or CASQ2 mutations.[7] Second, supraventricular arrhythmias, consisting of isolated atrial premature beat, SVT, and bursts of atrial fibrillation, are common in CPVT.[1] In addition, prominent U waves, dynamic in their appearance, are often found in CPVT patients, whose genesis and significance are not yet fully clarified. Finally, although a rare phenomenon, QT prolongation has been recently described in subjects with CPVT.[8] RyR2 gene mutation, which was detected in 6% of unrelated, genotype-negative long QT syndrome referrals, was hypothesized as responsible for arrhythmogenic after depolarizations of bradycardia-related acquired long QT syndrome.[9,10] These findings suggest that CPVT may be under-recognized among affected individuals because of a missed diagnosis. Thus, a diagnosis of “atypical long QT syndrome” may warrant suspicion of CPVT and the genetic analysis of RyR2, if the standard gene screen for long QT syndrome is negative. However, as the phases of QT prolongation in this case became present in the process of amiodarone treatment, it was unclear whether this phenomenon was directly related to the suffering disease or it was drug-induced.

CPVT is recognized as a genetic disease associated with pathogenic variants of calcium handling genes. Therefore, genetic testing is significant for diagnosis confirmation, particularly in atypical cases or asymptomatic carriers. To date, 6 disease-causing genes have been identified, and the inheritance patterns may be autosomal dominant (RyR2, KCNJ2, CALM1, and CALM2) or recessive (CASQ2 and TRDN). According to the current guidelines,[3] genetic testing was performed to this case, revealing a pathogenic mutation of RyR2 gene occurred in the patient. RyR2 variant is the most frequent form of CPVT, responsible for up to 82% of CPVT cases. However, this case had not been previously described in the literature.

Figure 3. The results of genetic sequencing that indicated a newly single mutant of RYR2 at c.7580T>G in absence of parents’ and sibling’s findings.
60% of the cases.\(^{[10]}\) RyR2 is a large channel-protein, located within the sarcoplasmic reticulum, which is a pivotal component of calcium homeostasis and associated excitation-contraction coupling in the cardiomyocyte.\(^{[11]}\) Genetic alterations in the RyR2 gene increase spontaneous diastolic calcium release from the sarcoplasmic reticulum, produce delayed afterdepolarization, and thereby trigger life-threatening ventricular arrhythmias under catecholaminergic stimulation.\(^{[12]}\) Since RyR2 mutations may be a cause of adrenergically mediated idiopathic ventricular fibrillation,\(^{[12]}\) we postulated that the ventricular fibrillation triggered by exercise testing might be in such instance, which was very rare in other CPVT cases. In addition, it was reported that patients with RyR2 CPVT became symptomatic earlier, remained symptomatic despite being treated, and was at higher risk of cardiac events in males;\(^{[2]}\) which is consistent with the clinical features of this case. Moreover, as the new mutant on RYR2 c.7580T>G found in our study could result in the alteration of encoded amino acid sequence, we hypothesized that the altered physiologically important conformation of RyR2 protein would render the channel more sensitive to stimuli, leading to channel dysfunction. The new mutant might shed some light on the understanding of RyR2 function and its roles in CPVT if it could be further confirmed in more clinical samples and unraveled through structure-function analysis.

Unfortunately, the missed and delayed diagnosis of the patient contributed to his recurrent arrhythmogenic episode. According to current guidelines,\(^{[3]}\) preventive and therapeutic strategies in this case were based on close follow-up, extreme sport restriction, reduction in exposure to stressful situations, and pharmacological treatment with beta-blockers. Remarkably, up to one-third of CPVT patients, even with appropriate use of beta-blockers, may experience recurrent cardiac events or manifest persistence of complex arrhythmias at exercise stress testing.\(^{[10]}\) Considering that the parents of the patient refused ICD implantation, compliance with exercise restriction and medical therapy should be emphasized to prevent recurrent cardiac events. Meanwhile, flecainide, showing direct RYR2 blocking properties,\(^{[13]}\) might be purchased from abroad. In addition, it is well known that renal sympathetic nerve (RSN) plays an important role in modulation of central sympathetic activity. RSN activation could increase cardiac and systemic sympathetic activity and promote the incidence of ventricular arrhythmias, suggesting renal sympathetic denervation (RSD) may be a potential alternative treatment modality for VT and it has been proved to be effective in several case reports and series.\(^{[14]}\) Recently, Akus et al.\(^{[15]}\) reported a case of successful catheter-based RSD in a 44-year-old man diagnosed with CPVT unresponsive to medical therapy and endocardial ablation procedure. This technique may be an alternative strategy in patients who refused ICD implantation like the present case. Nevertheless, to our knowledge, the efficacy of RSD in management of CPVT has merely been explored in adult patients, while no trials of RSD therapy have been described in children. Based on complexity of this procedure and less well-established evidence to qualify its efficacy in pediatric patients, RSD was not suggested to his parents in our study.

### 4. Conclusions

CPVT is a rare but potentially lethal inherited arrhythmia syndrome induced by adrenergic stress. A delay to diagnosis is substantial due to the low awareness and recognition of the condition and ignorance about the importance of genetic testing, which remain challenges to overcome in the future, particularly in developing countries. In despite of a normal baseline EKG and structurally normal heart, a more thorough clinical history, some features in baseline EKGs (e.g., sinus bradycardia, SVT, and phases of QT prolongation) and polymorphic and/or bidirectional VT induced by exercise or emotional stress can increase clinical suspicion. Exercise testing is essential in making the diagnosis of CPVT. Importantly, Genetic testing is a significant tool for a timely and accurate diagnosis of CPVT. The current study firstly reported a case with CPVT associated with a newly identified mutant of RYR2 at c.7380T>G in children.

### Author contributions

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