Clinical and genetic profile of catecholaminergic polymorphic ventricular tachycardia in Hong Kong Chinese children

TC Yu *, Anthony PY Liu, KS Lun, Brian HY Chung, TC Yung

ABSTRACT

Objective: To report our experience in the management of catecholaminergic polymorphic ventricular tachycardia in Hong Kong Chinese children.

Methods: This case series study was conducted in a tertiary paediatric cardiology centre in Hong Kong. All paediatric patients diagnosed at our centre with catecholaminergic polymorphic ventricular tachycardia from January 2008 to October 2014 were included.

Results: Ten patients (five females and five males) were identified. The mean age at presentation and at diagnosis were 11.0 (standard deviation, 2.9) years and 12.5 (2.8) years, respectively. The mean delay time from first presentation to diagnosis was 1.5 (standard deviation, 1.3) years. They presented with recurrent syncope and six patients had a history of aborted cardiac arrest. Four patients were initially misdiagnosed to have epilepsy. Catecholaminergic polymorphic ventricular tachycardia was diagnosed by electrocardiogram at cardiac arrest (n=2), or provocation test, either by catecholamine infusion test (n=6) or exercise test (n=2). Mutations of the *RyR2* gene were confirmed in six patients. Nine patients were commenced on beta-blockers after diagnosis. Despite medications, three patients developed aborted or resuscitated cardiac arrest (n=2) and syncope (n=1). Left cardiac sympathetic denervation was performed in five patients and an implantable cardioverter defibrillator was implanted in another. There was no mortality during follow-up.

Conclusions: Catecholaminergic polymorphic ventricular tachycardia should be considered in children who present with recurrent syncope during exercise or emotional stress. Despite beta-blocker treatment, recurrent ventricular arrhythmias occur and may result in cardiac arrest.

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[1] **TC Yu *,** MB, ChB, FHKAM (Paediatrics)
[2] **APY Liu,** MB, BS, MRCPCH
[3] **KS Lun,** MB, ChB, FHKAM (Paediatrics)
[2] **BHY Chung,** MB, ChB, FHKAM (Paediatrics)
[3] **TC Yung,** MB, BS, FHKAM (Paediatrics)

[1] *Department of Paediatrics and Adolescent Medicine, Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong*
[2] *Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong*
[3] *Department of Paediatric Cardiology, Queen Mary Hospital, Pokfulam, Hong Kong*

* Corresponding author: ytc604@ha.org.hk

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New knowledge added by this study

- This is the first study of catecholaminergic polymorphic ventricular tachycardia (CPVT) in Hong Kong describing local experience in the management of this rare arrhythmic syndrome.
- The genetic background (*RyR2* mutation) of our Chinese children is similar to those in overseas studies.

Implications for clinical practice or policy

- CPVT should be considered in young patients who present with exercise-related syncope.
- Maintaining a high index of suspicion and correct diagnosis of CPVT may be life-saving.

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia syndrome. Mutation of the ryanodine receptor 2 (*RyR2*) gene and infrequently the calsequestrin (*CASQ2*) gene is identified in approximately 60% to 70% of patients.[1,2] Patients with CPVT usually present with syncope and sudden cardiac death. The symptoms are due to bidirectional polymorphic ventricular tachycardia (VT) induced by adrenergic stress.[1] Onset of arrhythmia syndrome is usually in childhood. Many affected children are considered to have vasovagal syncope or epilepsy before a correct diagnosis is made.[1-4] If left untreated, the mortality of CPVT is up to 31% by the age of 30 years.[1,3,5]

In this study, we reviewed the clinical characteristics, genetic profile, and outcome of CPVT in Hong Kong Chinese children.

Methods

Our study included children diagnosed with CPVT from January 2008 to October 2014 at Queen Mary

Hospital, a university-affiliated teaching hospital in Hong Kong. The hospital records were retrospectively reviewed. Demographic data, clinical presentation, diagnostic methods, and genetic tests were reviewed. In all patients, the heart rate–corrected QT interval of the resting electrocardiogram was normal and the presence of structural heart disease was excluded by echocardiography (n=10) and/or magnetic resonance imaging (n=5). We also summarised the treatment modalities, response to treatment, and clinical outcome up to October 2014.

Genetic analysis

Blood samples of seven patients were sent to the Molecular Genetics Laboratory of Victorian Clinical Genetic Services, Australia where testing for mutations of the *RyR2* gene was performed. The assay involved sequencing of 17 hotspot exons (exons 1, 8, 14, 15, 44, 46, 47, 49, 88, 93, 95, 97, 101, 102, 103, 104, 105), their splice junctions and 20 bps into the introns. Since 2014, the Laboratory has made use of a cardiac next-generation sequencing panel to analyse the 28 arrhythmia genes: *AKAP9*, *ANK2*, *CACNA1C*, *CACNA2D1*, *CACNB2*, *CASQ2*, *CAV3*, *GJA5*, *GPD1L*, *HCN4*, *KCNA5*, *KCND3*, *KCNE1*, *KCNE1L*, *KCNE2*, *KCNE3*, *KCNH2*, *KCNJ2*, *KCNJ5*, *KCNJ8*, *KCNQ1*, *NPPA*, *RYR2*, *SCN1B*, *SCN3B*, *SCN4B*, *SCN5A*, and *SNTA1*. In two patients, the samples were tested by the local Laboratory Genetic Service (Department of Pathology, Princess Margaret Hospital, Hong Kong), where direct sequencing of selected hotspot exons and the flanking introns (10 bps) was performed. Cascade testing was offered for first-degree relatives of genotype-positive subjects.

香港華籍兒童中兒茶酚胺多形性心室心動過速的臨床和基因譜

余德政、廖栢賢、倫建成、鍾侃言、翁德璋

目的：報告我們治理兒茶酚胺多形性心室心動過速（CPVT）香港華籍兒童患者的經驗。

方法：本病例系列研究在香港一所三級兒科心臟病學中心內進行。研究對象包括2008年1月至2014年10月期間在上述中心確診CPVT的所有兒童。

結果：共有10名CPVT患者（5男5女），他們病發及確診的平均年齡分別為11.0歲（標準差2.9歲）和12.5（2.8）歲。病發至診斷的延誤期為1.5年（標準差1.3年）。所有患者出現反覆暈厥，其中6例曾出現心臟驟停的現象。4例最初被誤診為癲癇。有2例在心臟驟停期間作心電圖時才發現CPVT的症狀；其餘則在激發試驗當中因兒茶酚胺輸液測試（6例）或運動（2例）而確診。患者中6例證實有*RyR2*基因突變。9例患者確診後開始接受β受體阻滯劑的治療。儘管接受了藥物治療，3例仍出現中止或心臟驟停復甦（2例）和暈厥（1例）。5例接受左心交感神經切除術，另1例接受植入式心臟復律除顫器。隨訪期間並無死亡病例。

結論：當有兒童在運動期間或情緒緊張時反覆出現暈厥，便應考慮CPVT的可能性。儘管接受β受體阻滯劑的治療，復發性室性心律失常仍會發生，並可能導致心臟停頓。

Results

Characteristics of the study subjects

During the study period, 10 patients were diagnosed to have CPVT. Their demographic data and clinical

TABLE 1. Demographic data, clinical presentation, diagnostic method, and the threshold heart rate of polymorphic ventricular ectopic and ventricular tachycardia of the 10 patients

Patient No.	Sex	Age of onset (years)	Age at diagnosis (years)	Delay of diagnosis (years)	Follow-up duration (years)	Presentation	Diagnostic method	QTc interval of resting ECG (ms)	VE threshold (heart rate, beats/min)	VT threshold (heart rate, beats/min)
1	Male	6.2	6.9	0.7	6.7	Syncope	Isoprenaline infusion	426	120	140
2	Female	11.0	14.1	3.1	5.5	Syncope	Adrenaline infusion	394	110	142
3	Female	9.7	13.0	3.3	6.4	Syncope	Treadmill	416	150	150
4	Female	14.2	14.3	0.1	4.7	Aborted cardiac arrest	Arrest ECG	422	90	126
5*	Male	11.6	14.9	3.4	2.9	Syncope	Treadmill	406	125	NA
6	Female	7.2	9.2	2.0	2.7	Aborted cardiac arrest	Adrenaline infusion	396	110	166
7	Female	13.7	15.1	1.4	2.7	Syncope	Adrenaline infusion	444	126	170
8	Male	13.2	13.2	0	2.4	Aborted cardiac arrest	Adrenaline infusion	380	117	138
9*	Male	14.0	14.4	0.3	2.0	Aborted cardiac arrest	Arrest ECG	423	NA	NA
10	Male	9.3	10.0	0.7	0.7	Syncope	Adrenaline infusion	404	120	130

Abbreviations: ECG = electrocardiogram; NA = not available; QTc = heart rate–corrected QT; VE = ventricular ectopic; VT = ventricular tachycardia
* Brothers of the same family

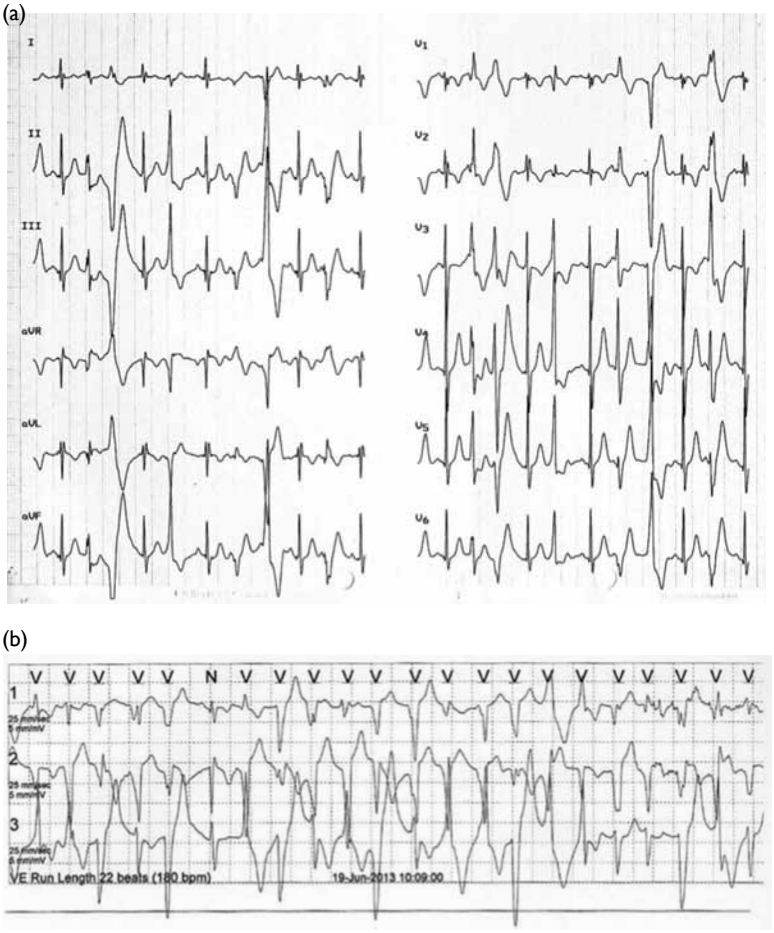

FIG. Patient 1: (a) polymorphic ventricular ectopics, with bidirectional QRS complexes induced by exercise test; and (b) polymorphic ventricular tachycardia, with bidirectional QRS complexes recorded by Holter monitoring

features are summarised in Table 1. The group comprised five female and five male patients; two of whom were brothers. The mean (± standard deviation) age at first presentation was 11.0 ± 2.9 (range, 6.2-14.2) years. The mean age at diagnosis was 12.5 ± 2.8 (range, 6.9-15.1) years. The mean delay time from first presentation to diagnosis was 1.5 ± 1.3 years.

Six patients presented initially with syncope while the other four presented with aborted cardiac arrest. At the end of the study, a total of six patients had aborted cardiac arrest. The triggering event for syncope or cardiac arrest was either exercise or emotion. Nonetheless, no such event was evident in three patients.

Four patients were initially misdiagnosed with epilepsy, one of whom was treated with an anticonvulsant prior to the diagnosis of CPVT.

Of the four patients who presented with aborted cardiac arrest, three required repeated cardioversion because of recurrent VT immediately following successful termination of ventricular arrhythmias. The case of patient 4 has been reported previously.[6]

Diagnosis of catecholaminergic polymorphic ventricular tachycardia and genetic analysis

Diagnosis of CPVT in two patients was based on the presence of bidirectional polymorphic VT in the cardiac arrest electrocardiogram. In the remaining patients, diagnosis was made when polymorphic or bidirectional VT was induced during provocation tests by exercise (n=2) or catecholamine infusion (n=6). Heart rate at the induction of ventricular premature beats ranged from 90 to 150 beats/min. Polymorphic VTs were induced when heart rate was increased to 126 to 170 beats/min (Fig).

Of the nine patients with genetic study, six were confirmed to have mutations of the *RyR2* gene as shown in Table 2. One patient (patient 9) did not undergo genetic study because his brother (patient 5) was confirmed to have no mutation of *RyR2*. Only two (brothers of the same family) of 10 patients had a family history of cardiac arrhythmic events. There was no *RyR2* mutation identified in the first-degree relatives of any patient with a *RyR2* mutation.

Treatment and response

Medical treatment

The treatment modalities and response are summarised in Table 3. All patients were started on a beta-blocker as first-line medication. One patient initially refused medical treatment. She then had recurrent syncope and subsequently agreed to treatment with nadolol.

Metoprolol was prescribed to three patients as initial medical treatment, although all switched to nadolol with or without flecainide due to unsatisfactory control (aborted cardiac arrest in one and exercise-induced polymorphic VT in another) or intolerable side-effects (tiredness and significant bradycardia at 38 beats/min).

Of the six patients prescribed nadolol as the first medication, five had no more syncope and no VT on treadmill exercise testing. Nadolol was changed to flecainide in one patient (patient 7) due to significant resting bradycardia of 35 beats/min. Nadolol was later resumed at a lower dose.

Atenolol was started in one girl as initial medical treatment but failed to prevent recurrent syncope. After changing to nadolol, she remained symptomatic and subsequently underwent left cardiac sympathetic denervation (LCSD).

Additional treatments

Left cardiac sympathetic denervation was performed via a video-assisted thoracoscopic approach in five

TABLE 2. *RyR2* mutations identified in our cohort

Patient No.	Detection method	Nucleotide change	Mutation	Novel
1	Sequencing of selected hotspot (exon 105)*	14848G>A	E4950K	No
2	NGS – arrhythmia panel	12475C>A	Q4159K	Yes
3	Sequencing of 17 hotspots	Negative	Negative	Not applicable
4	Sequencing of 17 hotspots	7420A>G	R2474G	Yes
5	Sequencing of 17 hotspots	Negative	Negative	Not applicable
6	Sequencing of selected hotspots (exons 3, 8, 14, 46, 47, 49, 88, 89, 90, 93, 97, 100, 101, 103)*	11836G>A	G3946S	No
7	Sequencing of 17 hotspots	Negative	Negative	Not applicable
8	Sequencing of 17 hotspots	14861C>G	A4954G	Yes
9	Not tested (as sibling tested negative)	-	-	-
10	NGS – arrhythmia panel	12475C>A	Q4159K	Yes

Abbreviation: NGS = next-generation sequencing

* Test performed in local Laboratory Genetic Service

TABLE 3. The medical and surgical treatment, most-severe arrhythmic events during follow-up, and the latest Holter or Treadmill results with current treatment of the 10 patients

Patient No.	*RyR2* mutation	Initial medical treatment	Current treatment	Most-severe arrhythmic event during follow-up	Resting heart rate at last follow-up (beats/min)	Latest Holter / Treadmill results with current treatment
1	Positive	Metoprolol 25 mg BD	Nadolol 60 mg daily + flecainide 50 mg BD + LCSD	Aborted cardiac arrest	39	Holter: still polymorphic VT at 182/min Treadmill: no exercise-induced tachyarrhythmia
2	Positive	Metoprolol 50 mg BD	Flecainide 100 mg/150 mg BD + LCSD	Nil	37	Holter: no VE or VT Treadmill: polymorphic VE (triplets), less sustained
3	Negative	Refused	Nadolol 40 mg daily	Syncope	53	Treadmill: much less polymorphic VEs, no VT
4	Positive	Atenolol 50 mg daily	Nadolol 40 mg daily + LCSD	Syncope	46	Treadmill (after LCSD): less frequent exercise-induced VEs; no VT
5	Negative	Nadolol 60 mg daily	Nadolol 60 mg daily	Nil	52	Holter: no VE or VT Treadmill: frequent monomorphic VE but no VT induced
6	Positive	Nadolol 60 mg daily	Nadolol 80 mg daily + LCSD	Nil	53	Holter and Treadmill with current treatment not performed yet at the end of study
7	Negative	Nadolol 10 mg daily	Nadolol 20 mg daily + flecainide 150 mg BD + ICD	Aborted cardiac arrest	59	Holter: no VE Treadmill: no exercise-induced VE
8	Positive	Metoprolol 50/75 mg BD	Nadolol 100 mg daily + flecainide 100 mg BD + LSCD	Nil	47	Treadmill: no VE or VT
9	Refused	Nadolol 80 mg daily	Nadolol 80 mg daily	Nil	62	Treadmill: no exercise-induced VE or VT
10	Positive	Nadolol 20 mg daily	Nadolol 80 mg daily	Nil	60	Treadmill: short runs of polymorphic VT (5 beats)

Abbreviations: BD = twice daily; ICD = implantable cardioverter defibrillator; LCSD = left cardiac sympathetic denervation; VE = ventricular ectopic; VT = ventricular tachycardia

patients. The lower half of the stellate ganglion and the sympathetic trunk of T2 to T4 were resected. After LCSD, one patient (patient 1) still had recurrent syncope. The other four patients had no more syncope. Dual-chamber implantable cardioverter defibrillator (ICD) implantation was performed in one patient (patient 7) who experienced an aborted cardiac arrest despite flecainide. She had no complications related to the ICD implantation. After implantation, she had one episode of syncope

while she was swimming slowly in the pool with her mother. She was taken out of the water and was able to stand unaided soon after. The ICD interrogation noted an episode of VT/ventricular fibrillation that was successfully aborted by electric shocks from the ICD. She had no inappropriate shocks from the ICD during the follow-up period of 30 months.

Outcomes

The median duration of follow-up was 3.7 ± 2.0 (range, 0.7-6.7) years. Six (60%) patients became asymptomatic after drug treatment. Two patients had recurrent syncope; one of whom was without drug treatment. Two patients experienced aborted cardiac arrest, one received ICD implantation and another one refused. There was no mortality during the study period.

Discussion

Catecholaminergic polymorphic ventricular tachycardia is uncommon in Hong Kong Chinese children. Our centre treated most of the serious local paediatric cardiac arrhythmia cases. Over a period of 7 years we identified only 10 patients. Our case series is, to date, the largest in Chinese children.

Many of our patients (6 out of 10) had experienced aborted cardiac arrest as the near-fatal arrhythmic event during the study. The diagnosis of CPVT can be challenging and requires documentation of typical bidirectional polymorphic VT at presentation, or induction of polymorphic VT by exercise test or catecholamine infusion test.[1-3,7,8] Studies show that diagnosis of CPVT can be made in 69% and 75% of patients by exercise test and catecholamine infusion test, respectively.[9,10]

Misdiagnosis and delay in diagnosis of CPVT is common. Our patients had a mean delay of 1.5 years from first presentation to diagnosis. Four of our patients were initially misdiagnosed with epilepsy, one of whom was prescribed anticonvulsant therapy. Of the 10 patients, four were not diagnosed until they presented with aborted cardiac arrest.

Genetic mutations are identified in 60% to 70% of patients with CPVT, and more than 90% of the mutations affect the *RyR2* gene.[1,3] Mutation of the *CASQ2* gene is rare (<2%). Very recently, mutation of triadin, a transmembrane sarcoplasmic reticulum protein, was found to be the cause of CPVT in two families.[11] In these mutations, the defective proteins cause excessive calcium release from the sarcoplasmic reticulum to the cytoplasm leading to polymorphic VT.[1,5] Similar to overseas studies, mutation of the *RyR2* gene was evident in the majority (60%) of our patients.

Patients with CPVT must be restricted from exercise to avoid the adrenergic trigger. A beta-blocker serves as first-line medical therapy.[1,2,4,10] Nonetheless, CPVT is a very malignant arrhythmic disease and many patients remain symptomatic despite such therapy.[1,3,4,10] In a systematic analysis of 354 CPVT patients treated with beta-blockers, the estimated 8-year arrhythmic event rate was 37.2%.[12] Our study also showed that a high proportion of patients still developed arrhythmic events despite beta-blocker treatment (syncope in one and aborted cardiac arrest in two out of 10 patients).

In the early period of study, we prescribed metoprolol in three patients, although all experienced treatment failure due to recurrent symptoms or intolerance. In the later period, nadolol was the initial medication and five out of six patients became asymptomatic.

Flecainide, a class 1c anti-arrhythmic drug with dual action of direct ryanodine receptor blockage and blockage of sodium channels,[1,12] may be effective in CPVT patients. Flecainide has been evaluated in a multicentre study of 33 CPVT patients. In 22 (76%) out of 29 patients, flecainide suppressed exercise-induced ventricular arrhythmia either partially (n=8) or completely (n=14).[1,12,13] In our study, flecainide was used in four patients who had failed treatment with a beta-blocker. Three patients still had arrhythmic events, however.

Studies showed that LCSD, which prevents noradrenaline release in the heart, is highly effective in severely affected CPVT patients.[14,15] It can be performed with a minimally invasive approach by video-assisted thoracic surgery. In our study, five patients underwent LCSD. All recovered well and no complications were noted at follow-up. Four had no more syncope. Large studies are needed to further evaluate its efficacy in CPVT patients.

An ICD has been recommended in patients who fail optimised medical therapy.[1,12,14,16] Some recent studies have suggested that ICD may be harmful to CPVT patients, however, because both appropriate and inappropriate ICD shocks can potentially induce VT storms and cardiac arrest.[16,17] Therefore, ICD implantation should be restricted to patients with symptoms refractory to optimised medical treatment and LCSD.[18]

Conclusions

Catecholaminergic polymorphic ventricular tachycardia is an uncommon but malignant cardiac arrhythmia that presents as syncope, seizure, or sudden cardiac death in childhood. In our study, 60% of patients experienced aborted cardiac arrest. One should suspect the diagnosis when syncope occurs during exercise or emotional stress. Similar to overseas studies, *RyR2* mutation is the most common genetic mutation and affected 60% of our patients. Despite optimised medical therapy, 60% of patients still required LCSD or ICD implantation.

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Declaration

All authors have no relevant conflicts of interest to disclose.

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