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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.

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. 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. 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. If left untreated, the mortality of CPVT is up to 31% by the age of 30 years.

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, KCN4, KCN5, KCNE1, KCNE2, KCNE3, KCN2, KCN5, KCN4, KCNQ1, NPPA, PYK2, 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.

Results

Characteristics of the study subjects

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

### TABLE 2. RyR2 mutations identified in our cohort

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

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

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

Abbreviations: BD = twice daily; ICD = implantable cardioverter defibrillator; LCSD = left cardiac sympathetic denervation; VE = ventricular ectopic; VT = ventricular tachycardia
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. Studies show that diagnosis of CPVT can be made in 69% and 75% of patients by exercise test and catecholamine infusion test, respectively.

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. 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. In these mutations, the defective proteins cause excessive calcium release from the sarcoplasmic reticulum to the cytoplasm leading to polymorphic VT. 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. Nonetheless, CPVT is a very malignant arrhythmic disease and many patients remain symptomatic despite such therapy. In a systematic analysis of 354 CPVT patients treated with beta-blockers, the estimated 8-year arrhythmic event rate was 37.2%. 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, 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). 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. 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. 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. Therefore, ICD implantation should be restricted to patients with symptoms refractory to optimised medical treatment and LCSD.

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.
Acknowledgements
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Declaration
All authors have no relevant conflicts of interest to disclose.

References