Clinical Characteristics, Genetic Findings and Arrhythmic Outcomes of Patients with Catecholaminergic Polymorphic Ventricular Tachycardia from China

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Abstract: Introduction: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare cardiac ion channelopathy. The aim of this study is to examine the clinical characteristics, genetic basis and arrhythmic outcomes of CPVT patients from China. Methods: PubMed and MedRxiv were systematically searched for case reports or case series reporting on CPVT patients from China. Clinical characteristics, genetic findings and primary outcome of spontaneous ventricular tachycardia/ventricular fibrillation (VT/VF) were analyzed. Results: A total of 56 (median presentation age=9 [6-13] years old) patients were included. All patients except for one presented at or before 19 years of age. Fifty-three patients (94.6%) were initially symptomatic. PVCs were present in 40 out of 45 patients (88.9%) and VT in 51 out of 56 patients (91.1%). Genetic tests were performed in 50 patients (89.3%) with a yield of 76.8%. RyR2, CASQ2 and TERCL mutations were found in 32 (57.1%), 11 (19.6%) and one (0.02%) patients, respectively. Fifty patients were treated with beta-blockers, eight patients received flecainide, four patients received amiodarone, two received verapamil and one received propafenone. Sympathectomy (n=10) and implantable-cardioverter defibrillator implantation (n=7) were performed. On follow-up, 17 patients developed incident VT/VF. Conclusion: This is the first systemic review and meta-analysis of CPVT patients from China. Most patients had symptoms on initial presentation, and around a third had VT as the presenting complaint. RyR2 mutation accounts for more than half of the CPVT cases, followed by CASQ2 and TERCL mutations. Some of these mutations have not been hitherto reported outside of China. Most patients received β-blocker therapy. Around 18% had sympathectomy and 13% had ICDs implanted.
1. Introduction

Cardiac ion channelopathies predispose to the development of spontaneous ventricular tachycardia/ fibrillation (VT/VF) and sudden cardiac death (SCD) [1-6]. Of these, catecholaminergic polymorphic ventricular tachycardia (CPVT) is a less prevalent condition compared to Brugada syndrome (BrS) in Asia [7, 8]. It is typically caused by mutations in either the ryanodine receptor 2 (RyR2) [9] or the calsequestrin 2 (CASQ2) [10, 11], but mutations in other genes such as calmodulin (CALM) have been implicated [12-14]. CPVT is usually precipitated by exercise or distress, which results in bidirectional VT, presenting in the first two decades of life [15]. Globally, population-based data on CPVT have mainly come from Western countries. The largest registry created by the Pediatric and Congenital Electrophysiology Society of the United States reported the characteristics of 237 patients [16, 17]. In another multi-national study including mainly patients from France, outcomes in 101 patients were reported [18], complementing smaller registry and case series studies by the same group [19, 20]. Another study reported specifically 21 CPVT patients caused by the CALM genes [12].

By contrast, data from Asia have been relatively sparse. A multi-centre Japanese registry of 78 patients found that 94% of the cases were sporadic with only 6% of the cases being familial [21]. In a national study from Japan, it was found that 30 gene mutation carriers were found for three genes in 50 probands [22]. Another Japanese reported on the findings of 29 patients [23]. However, to date, case descriptions from China have been limited to case series [11, 24-26] and there is no established registry nationally. Moreover, many of these reports are published in Chinese, and have limited accessibility to researchers beyond the country. Therefore, the aim of this study is to identify cases from a systematic search of the literature and synthesize evidence on clinical characteristics, genetic basis and arrhythmic outcomes of CPVT patients from China.

2. Methods

2.1. Study Population

PubMed and MedRxiv were systematically searched for case reports or case series that described CPVT patients from China, which allowed a primary synthesis of cases for analysis. Where overlapping cohorts were described, data were extracted from the publication with the largest cohort. Diagnosis of CPVT was established based on the exercise treadmill test, adrenaline challenge test, or genetic testing as defined by the individual papers. The individual cases were analyzed according to diagnostic criteria proposed by the 2013 Heart Rhythm Society (HRS)/ European Heart Rhythm Association (EHRA)/ Asia-Pacific Heart Rhythm Society (APHRS) expert consensus statement (Supplementary Table 1) [27]. All genetic mutations described in the studies were compared to those in the published literature [16, 28-31], in order to determine their possible pathogenicity and novelty.

2.2. Data Extraction

The following clinical data were extracted from the published studies: 1) sex, 2) age of presentation, 3) age of diagnosis, 4) family history of SCD or CPVT, 5) initial symptoms, initial presentation with 6) syncope, 7) palpitations, 8) chest pain or 9) seizures, the presence of 10) premature ventricular complexes (PVCs) or 11) ventricular tachycardia/ventricular fibrillation (VT/VF) detected on electrocardiography, Holter or exercise stress testing, 12) genetic testing, 13) methods of testing, 14) genetic results and 15) interpretation of the variants, 16) performance of 24-hours Holter study, exercise stress testing, electrophysiological study (EPS) and their respective results; 17) performance of echocardiogram and cardiac magnetic resonance imaging and results; 18) presence of bradycardic complications; 19) the presence of arrhythmias other than PVCs/VT/VF, 20) prescription of pharmacological agents and 21) implantation of implantable cardioverter-defibrillator (ICD).
2.3. Statistical Analysis

Categorical variables were summarized as frequency (%) and continuous variables were expressed as median (Q1-Q3). All statistical analysis was performed using Stata (Version: 16).

3. Results

Clinical characteristics, genetic findings and treatment

A systematic search of the PubMed and MedRvix databases yielded 1049 and 12 articles, respectively. After the exclusion of overlapping cohorts, a total of 56 unique cases from six cities by 11 studies were included [11, 25, 32-40]. Their clinical characteristics and test results are shown in Table 1. 21 patients fulfilled at least two criteria and 37 patients fulfilled one criterion of the 2013 HRS/EHRA/APHRS expert consensus statement (Supplementary Table 1). Twenty 20 (35.7%) patients were female and all patients were of Han Chinese origin. All patients except for one presented at or before 19 years of age. The median values (interquartile rate [IQR]) of the age of presentation and age of diagnosis were 9.0 (6.4-12.9) and 10.1 (9.0-13.0) years old respectively, with a median delay of 12 (2-36) months. 53 patients (94.6%) were initially symptomatic. PVCs were present in 40 out of 45 patients and VT in 51 out of 56 patients.

Genetic tests were performed in 50 patients (89.3%). RyR2, CASQ2 and TERCL mutations were found in 32 (57.1%), 11 (19.6%) and 1 (0.02%), respectively (Table 2). The c.14861C>G mutation is novel and has not been described beyond China [25].

Pharmacological and non-pharmacological treatments for this cohort are summarized in Table 3. Fifty patients were treated with β-blocker, eight patients received flecainide, four patients received amiodarone, two received verapamil and one received propafenone. Sympathectomy (n=10) and ICD implantation (n=7) were performed. On follow-up, 17 patients developed incident VT/VF.

Table 1. Baseline clinical and demographic characteristics of CPVT patients from China.

| Characteristic                | Median (Q1-Q3) / frequency (%) | Test                        | Median (Q1-Q3) / frequency (%) |
|------------------------------|--------------------------------|-----------------------------|--------------------------------|
| Female                       | 20 (35.7)                      | Echocardiogram              | 35 (62.5)                      |
| Presentation Age (years)     | 9.0 (6.4-12.9)                 | Abnormal echocardiogram     | 4 (11.4)                       |
| Diagnosis Age (years)        | 10.1 (9.0-13.0)                | Cardiac MRI performed       | 6 (10.7)                       |
| Presentation to Diagnosis (months) | 12 (2-36)                  | Abnormal cardiac MRI        | 0 (0)                          |
| Family History of CPVT/SCD   | 15 (30.6)                      | Genetic Test                | 50 (89.3)                      |
| Initially symptomatic        | 53 (98.1)                      | Positive Genetic Test       | 43 (76.8)                      |
| Initial syncope              | 51 (94.4)                      | Adrenaline Challenge        | 7 (12.5)                       |
| Initial VT/VF/SCD            | 17 (35.4)                      | Positive Adrenaline Challenge | 7 (100)                      |
| Initial palpitations         | 11 (30.6)                      | Exercise Tolerance Test     | 46 (82.1)                      |
| Initial chest pain           | 8 (22.2)                       | Positive Exercise Tolerance Test | 44 (95.7)          |
| Initial seizure              | 16 (36.4)                      | EPS                         | 3 (5.4)                        |
| PVC                          | 40 (88.9)                      | Positive EPS                | 3 (100)                        |
| VT/VF                        | 51 (91.1)                      | Holter Study                | 41 (73.2)                      |
| VT/VF post-presentation       | 17 (31.5)                      | Arrhythmia in Holter Study  | 31 (75.6)                      |
Table 2. Genetic test results.

| Gene   | Mutation | Region in Genome | Coding Effect | Mutation type | Mutation Hotspots for RyR2 | Pathogenicity | Predictions | Novel Mutation outside China | Reference               |
|--------|----------|------------------|---------------|---------------|----------------------------|---------------|-------------|-------------------------------|-------------------------|
| RyR2   | c.229C>T | Exon 3           | P77S          | Substitution  | Domain I                   | VUS           | VUS         | Not applicable                | Ge 2017                 |
| RyR2   | c.490C>T | Exon 8           | P164S         | Substitution  | Domain I                   | VUS           | Likely Pathogenic              | No: [58]                | Lin 2018                 |
| RyR2   | c.1639A>C | Exon 17          | N547H         | Substitution  | Non-hotspot                | VUS           | VUS         | Not applicable                | Ge 2017                 |
| RyR2   | c.2410C>T | Exon 22          | L804F         | Substitution  | Non-hotspot                | Likely benign | Benign      | RCV000639160.2                | Ge 2017                 |
| RyR2   | c.7202G>A | Exon 47          | R2401H        | Substitution  | Domain II                  | Likely Pathogenic | Pathogenic   | No: [41]                     | Lee 2021                |
| RyR2   | c.7258A>G | Exon 50          | L2527W        | Substitution  | Domain II                  | VUS           | VUS         | Not applicable                | Duan 2018               |
| RyR2   | c.10046C>T | Exon 69          | S3349L        | Substitution  | Non-hotspot                | VUS           | VUS         | No: [30, 42]                 | Lee 2021                |
| RyR2   | c.11836G>A | Exon 88         | G3946S        | Substitution  | Domain III                 | Pathogenic    | VUS         | No: [43, 46]                 | Ge 2017, Lee 2021       |
| RyR2   | c.12014A>T | Exon 90          | E4005V        | Substitution  | Domain III                 | VUS           | VUS         | Not applicable                | Yang 2021               |
| RyR2   | c.12272C>T | Exon 90          | A4091V        | Substitution  | Domain III                 | VUS           | VUS         | RCV00182811.1                | Yang 2021               |
| RyR2   | c.12475C>A | Exon 90          | Q4159K        | Substitution  | Domain III                 | VUS           | Likely Pathogenic              | No: [44]                | Lee 2021                 |
| RyR2   | c.13933T>C | Exon 96          | W4645R        | Substitution  | Domain IV                  | VUS           | VUS         | No: [45]                     | Ge 2017                 |
| RyR2   | c.14159T>C | Exon 97-99       | L4720P        | Substitution  | Domain IV                  | VUS           | VUS         | RCV000182842.2                | Lee 2021                |
| RyR2   | c.14570T>G | Exon 101         | I4857S        | Substitution  | Domain IV                  | VUS           | VUS         | Not applicable                | Ge 2017                 |
| RyR2   | c.14593C>A | Exon 101-102     | L4865I        | Substitution  | Domain IV                  | VUS           | VUS         | Not applicable                | Ge 2017                 |
| CASQ2  | c.97C>T  | Exon 1           | R33X          | Substitution  | Not applicable              | Likely Patho- genic | Pathogenic  | No: [59]                     | Gao 2018, Li Q 2019    |
| CASQ2  | c.98G>A  | Exon 1           | R33Q          | Substitution  | Not applicable              | VUS           | VUS         | No: [60]                     | Li Q 2019               |
| CASQ2  | c.244C>T | Exon 1           | Q82X          | Substitution  | Not applicable              | VUS           | Pathogenic | Not applicable                | Ge 2017                 |
| CASQ2  | c.532+1G>A | IVS              | Splice site mutation | Not applicable | VUS           | Pathogenic | Not applicable | Li Q 2019 |
| CASQ2  | c.748C>T | Exon 7           | R250C         | Substitution  | Not applicable              | VUS           | VUS         | RCV000694480.2                | Gao 2018, Li Q 2019    |
| Gene  | RefSeq | Exon/Region | Mutation Type   | Clinical Description |Clinical Implication | GenoReferencer |
|-------|--------|-------------|-----------------|----------------------|---------------------|-----------------|
| CASQ2 | c.838+1G>A | IVS | Splice site mutation | Not applicable | VUS | Pathogenic | Not applicable | Li Q 2019 |
| CASQ2 | c.1074_1075delinsC | Exon 11 | E359Rfs*12 | Deletion and insertion | Not applicable | VUS | Pathogenic | Not applicable | Li Q 2019 |
| CASQ2 | c.1175_1178delAC AG | Exon 11 | D392Vfs*84 | Deletion | Not applicable | VUS | Pathogenic | Not applicable | Li Q 2019 |
| TECRL | c.587C>T | Exon 6 | R196Q | Substitution | Not applicable | VUS | VUS | Not applicable | Xie 2019 |
| TECRL | c.918+3T > G | IVS | Splice site mutation | Not applicable | VUS | VUS | Not applicable | Xie 2019 |
Table 3. Management for CPVT patients in China.

| Treatment       | Frequency (%) |
|-----------------|---------------|
| β-blocker       | 50 (89.2)     |
| Verapamil       | 2 (3.6)       |
| Amiodarone      | 4 (7.1)       |
| Flecainide      | 8 (14.3)      |
| Propafenone     | 1 (1.8)       |
| Sympathectomy   | 10 (17.9)     |
| ICD implantation| 7 (12.5)      |

4. Discussion

This is the systematic review and meta-analysis of published cases on CPVT patients from China. There are several novel findings from the present study: 1) RyR2 mutations account for over half of the CPVT cases, 2) 20 RyR variants, seven CASQ2 variants and two TERCL variants were described, 3) β-blocker are used in 89.2% of the cases, followed less frequently by flecainide, amiodarone, verapamil and propafenone, and 4) 17.9% patients underwent cardiac sympathectomy and 12.5% received ICDs.

Sudden cardiac death is an important clinical problem globally, with congenital and acquired causes [47-50]. Of the congenital cardiac ion channelopathies, CPVT is characterized by exercise-induced bidirectional VT. International registry studies on European and North American patients have reported that there is a malignant arrhythmic phenotype associated with this disease with significant delays between initial presentation and subsequent diagnosis of around six months [17, 51]. By contrast, the epidemiology and characteristics of studies in Asia are limited. In China, cases of CPVT have been limited to small case reports or case series. In this study, we performed a systematic search of the published literature, identifying CPVT cases that have been reported in the following cities: Beijing (n=22) [11, 32-34], Hong Kong (n=16) [25], Guangzhou (n=8) [35, 40], Nanjing (n=6) [36], Shanghai (n=3) [37, 38] and Sichuan (n=1) [39].

Several studies have examined the occurrence of adverse outcomes in CPVT cohorts, with particular emphasis on syncopal events and SCD [18, 19, 52, 53]. There is existing evidence to suggest that subjects who are initially symptomatic, as similarly shown in our study, as well as those who are younger at diagnosis and are not administered β-blocker therapy have a significantly higher risk of cardiac events, including syncope, aborted cardiac arrest, and/or sudden cardiac death [18]. Likewise, findings indicate that an initial symptomatic presentation and an absence of β-blocker administration have also shown to be associated with mortality in CPVT patients [18]. Regarding electrocardiographic parameters, there is a relative paucity in literature assessing their use in risk prediction for VT/VF in the setting of CPVT. However, in the context of SCD as outcome, despite the fact that some reports studying its relationship with ECG variables have demonstrated significant differences in the QRS duration of recorded PVCs between patients who remained alive and those who suffered SCD during follow-up, most other ECG variables, such as those investigated in our study, namely heart rate and QTc interval, failed to demonstrate any notable variations with time [18].

Regarding the genetic basis, this study identified 20 RyR variants. Of these, 12 have been reported outside China: c.490C>T [58], c.2410C>T (RCV000639160.2), c.7202G>A [41], c.7258A>G [31], c.7420A>G [28], c.10046C>T [30, 42], c.11836G>A [43, 46], c.12272C>T (RCV00182811.1), c.12475C>A [44], c.13933T>C [45], c.14159T>C (RCV000182842.2), c.14848G>A [46]. By contrast, c.14861C>G is a novel RyR2 variant that gives rise to the A4954G amino acid change [25]. This mutation affects the cytoplasmic domain of the RyR2, is expected to produce abnormalities in calcium handling, possible diastolic calcium leak and triggered arrhythmogenesis [54]. However, functional studies are...
needed to determine the precise mechanisms by which this structural change can lead to the generation of an electrophysiological substrate. Previous animal studies have reported that the RyR2 mutations can be associated with not only disrupted calcium homeostasis but also reduced conduction velocity [55-57].

CASQ2, in comparison, accounts for a fewer proportion of CPVT cases. In our study, 8 variants were reported. Three have been reported from publications arising from outside China: c.97C>T [59] c.98G>A [60], and c.748C>T (RCV000694480.2), with six novel mutations. The two TERCL variants reported in our study are also novel mutations. Finally, CALM2 has also been implicated in CPVT but our study did not identify mutations in this gene.

Strengths and limitations

The major strengths of the present study include extraction and integration of data which allows easier interpretation by researchers beyond China and a comprehensive analysis of clinical characteristics, genetic basis and arrhythmic outcomes of CPVT patients from China.

The major limitation of the present study is that data was extracted from case reports or case series. Without a national registry, cases reported may not include all the domains that were assessed in this current study, therefore the data may not reflect the actual picture of CPVT patients from China especially regarding arrhythmic events on follow-up.

5. Conclusion

This is the first systemic review and meta-analysis of CPVT patients from China. Most patients had symptoms on initial presentation, and around a third had VT as the presenting complaint. RyR2 mutation accounts for more than half of the CPVT cases, followed by CASQ2 and TERCL mutations. Some of these mutations have not been hitherto reported outside of China. Most patients received β-blocker therapy. Around 18% had sympathectomy and 13% had ICDs implanted.

Contributor statement: Sharon Lee, Justin Leung, and Gary Tse: study conception, data acquisition, database building, statistical analysis, manuscript drafting, manuscript revision

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