

Article

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 8) 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 MedRxiv 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 48	R2420G	Substitution	Domain II	VUS	VUS	No: [31]	Ge 2017
RyR2	c.7420A>G	Exon 49	R2474G	Substitution	Domain II	VUS	Likely Pathogenic	No: [28]	Lee 2021
RyR2	c.7580T>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	Pathogenic	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
RyR2	c.14834A>G	Exon 105	Q4945R	Substitution	Domain IV	Likely benign	VUS	Not applicable	Ge 2017
RyR2	c.14848G>A	Exon 105	E4950K	Substitution	Domain IV	VUS	Likely Pathogenic	No: [46]	Lee 2021
RyR2	c.14861C>G	Exon 105	A4954G	Substitution	Domain IV	VUS	VUS	Not applicable	Lee 2021
CASQ2	c.97C>T	Exon 1	R33X	Substitution	Not applicable	Likely Pathogenic	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

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_1178delACAG	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: Sharen Lee, Justin Leung, and Gary Tse: study conception, data acquisition, database building, statistical analysis, manuscript drafting, manuscript revision

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