Catecholaminergic polymorphic ventricular tachycardia

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Abstract Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmogenic disorder that causes syncopal episodes related with stress or emotion and even sudden cardiac deaths. Signs and symptoms usually begin in childhood. A suspicion of CPVT should be kept in mind when a child or an adolescent suddenly loses consciousness, particularly if this happens upon physical exercise or sudden mental stress. During the past decade, the knowledge of CPVT genetics and physiology has increased. Exercise testing is essential when suspecting arrhythmogenic origin of syncope, and in the case of CPVT, it may be even more sensitive than Holter monitoring. Beta-antiadrenergic medication can substantially decrease the mortality associated with CPVT. Asymptomatic patients with known CPVT gene defects should also be treated because sudden cardiac death may be the first manifestation of the disease. An implantable cardioverter-defibrillator may also be required in the most severe CPVT cases. In this review, we summarise the current knowledge on the clinical characteristics, diagnostic, genetic and prognostic features of CPVT in children. In all, 133 publications covering 60 years were checked, and those

written in English and containing ten or more, mainly paediatric CPVT cases, were included. In addition, a CPVT family with three members and delayed diagnoses until late childhood and adulthood is presented.

Keywords Arrhythmia · Catecholaminergic polymorphic ventricular tachycardia · Childhood · Syncope

Introduction

Syncopal spell is a common symptom in children. When evaluating its cause, a detailed event history and the observations by the eyewitnesses are often useful. Often, the preceding events and symptoms are compatible with a harmless vasovagal collapse. However, a syncopal spell associated with physical effort should raise a suspicion of a cardiac disorder. If the loss of consciousness is associated with convulsions, it may be misdiagnosed as epilepsy if a prolonged circulatory arrest resulted in brain ischaemia. Most structural heart diseases can be diagnosed or ruled out with echocardiography. A 12-lead electrocardiography (ECG) can reveal an underlying arrhythmogenic disorder such as long QT syndrome (LQTS) or Brugada syndrome [3, 4, 14]. However, a syncopal spell associated with physical exercise or emotional stress may be of arrhythmogenic origin despite normal findings in physical examination, ECG and echocardiography [9].

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare but highly malignant inherited arrhythmia disorder. It is characterised by ventricular tachycardia (VT) which is polymorphic or bidirectional and induced by catecholamines triggered by physical exercise or emotional stress, typically in the absence of a structural heart disease [1, 2, 6, 8, 9, 11, 12, 16, 19]. Sudden cardiac death may be

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the first manifestation of CPVT [1, 19]. A standard resting ECG is usually normal [2, 6, 9, 11, 16]. An exercise stress test is essential if CPVT is suspected by symptom history.

For this review, we searched the Ovid Medline database for presumptive CPVT cases using the keyword “catecholaminergic polymorphic ventricular tachycardia”, covering the 60-year time period from 1950 to March 2009. In all, 133 hits were obtained. All abstracts were checked, and a total of seven original articles written in English with ten or more CPVT cases, consisting mainly of paediatric patients, were included in the review [1, 2, 6, 9, 11, 12, 16].

Clinical presentation

Signs and symptoms of CPVT begin usually in childhood (Table 1). They include palpitations, dizziness and even convulsions, and typically, there is a syncopal spell triggered by physical exercise or emotional stress [2, 9, 11, 12]. The mean age of symptom onset has varied from 7 to 9 years, although a later onset has also been reported [1, 2, 6, 9, 11, 16, 19]. Despite the clearly presumptive symptoms, sometimes the diagnosis may be missed or delayed [1, 2, 9, 12]. Many CPVT patients have been considered to have only a vasovagal syncope with no need

for further studies [1, 9, 12], some to have epileptic seizures [9, 11, 12], and some to have “LQTS with normal QT” [2, 9, 12] before the diagnosis of CPVT has been made. Approximately 30% of the patients have a positive family history of stress-related syncope, epileptic seizures or sudden death [9, 10, 12].

Diagnostic studies and differential diagnosis

A standardised exercise stress test is the most reliable way to diagnose CPVT [2, 6, 11, 16, 19]. Ventricular arrhythmias appear when the sinus rate exceeds an individual threshold rate, usually at a heart rate of 110–130 bpm [1, 2, 6, 9, 11, 16], as summarised in Table 1. The arrhythmias become more complex when the sinus rate further increases [9, 19] and consist of premature ventricular complexes (PVC), couplets, bigeminy and bidirectional or polymorphic VTs, often appearing in this order. When the exercise stress test is discontinued, arrhythmias gradually disappear [9, 19]. These arrhythmias do not usually compromise haemodynamics. Syncope or sudden death in CPVT is a consequence of more rapid or sustained ventricular tachycardia or ventricular fibrillation [9, 11]. Some CPVT patients may not have arrhythmias in the

Table 1 Summary of the studies published on catecholaminergic polymorphic ventricular tachycardia in children

Authors	Number of patients (female/male)	Age at onset (years) ^a	Age at diagnosis (years) ^a	Follow-up time (years) ^a	Heart rate at rest (bpm) ^a	Threshold frequency (bpm) ^a		Mortality among the probands	Genetic defect
						Onset of ventricular premature complexes	Onset of ventricular tachycardia		
Leenhardt et al. 1995	21 9/12	3–16	3.5–16.5	2–16	42–75	105–150	NA	2/21	NA
Lahat et al. 2001	13 9/4	3.5–12	0.25–25	1.5	47–90	90–123	90–123	0	Chromosome 1p13-21 (recessive) ^b
Priori et al. 2002 ^c	30 17/13	2–38	15±10	4±2.5	NA	NA	NA	NA	RyR2 gene mutations
Sumitomo et al. 2003	29 (16/13)	2–30	NA	6.8±4.9	59±11	NA	79–214	7/29	NA
Allouis et al. 2005	11 (9/2)	6–27	5–39	NA	NA	110–160	NA	2/11	RyR2 gene mutation
Postma et al. 2005 ^c	12 (9/3)	4–51	NA	2–28	43–73	NA	90–150	1/12	RyR2 gene mutations
Celiker et al. 2009	16 5/11	4.5–12	5–15	1–9	45–60	70–140	115–160	4/16	RyR2 gene mutation ^d

NA not available

^a Mean or ranges

^b *CASQ2* gene mutation was later found in chromosome 1p13-21 [7]

^c Priori and Postma expanded their studies from the original probands also to their families, but only the original probands are included

^d Verified in one child who experienced a sudden death. Genetic studies of the others are incomplete

exercise stress test during early childhood, but the change in the phenotype occurs later in life [17, 19]. Therefore, a regular follow-up with repeated exercise stress tests is indicated, e.g. for younger siblings of a CPVT patient. Progressive ventricular arrhythmias may also be provoked in some cases by intravenous infusion of catecholamines like adrenaline [2, 6, 9, 12, 16]. Echocardiography is needed to exclude structural heart disease, e.g. tumours of the heart, coronary anomalies or different cardiomyopathies, which do not present with murmurs. For the CPVT diagnosis, electrolyte abnormalities should be excluded, as well as the use of any drugs known to trigger arrhythmias. The 24-h Holter monitoring may reveal arrhythmias typical for CPVT if the sinus rate of the patient exceeds the individual arrhythmia-inducing threshold during monitoring. The 24-h Holter monitoring can be very useful in young, physically active children who are not yet able to perform exercise stress test. Symptoms and findings in CPVT are summarised in Table 2.

Other inherited arrhythmogenic cardiac disorders that can cause malignant ventricular tachyarrhythmias should also be excluded. The clinical characteristics and the typical resting ECG findings in the common inherited arrhythmogenic cardiac disorders are presented in Table 3. Exercise-induced, highly reproducible polymorphic VT is one of the diagnostic criteria of CPVT. The 12-lead resting ECG is usually within normal limits, though a relative sinus bradycardia or prominent U waves may be seen as non-specific findings [2, 6, 9, 11, 16]. CPVT patients may have

a slight prolongation of the corrected QT interval in the resting ECG, however not exceeding 470 ms [19], and there is no prolongation of the QT interval during exercise [12, 16]. In the patients with LQTS, the corrected QT interval is usually more than 460 ms, and they develop arrhythmias during exercise stress test infrequently [4]. The corrected QT interval shorter than 320 ms raises a suspicion of the short QT syndrome [15]. Exercise-provoked arrhythmias may develop also in arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), but the typical ECG pattern of ARVD/C and the structural abnormalities of the right ventricle separate ARVD/C from CPVT [19]. The typical arrhythmia in ARVD/C is the monomorphic VT with left bundle branch block pattern that is clearly different from the polymorphic PVCs or VT in CPVT. Patients with Brugada syndrome do not manifest polymorphic PVCs upon physical effort either, and the absence of the right bundle branch block and the ST segment elevations in the precordial ECG leads after provocation testing with sodium channel blocking agent, e.g. flecainide, make Brugada syndrome very unlikely [3, 14]. Arrhythmias in Brugada syndrome appear usually at rest or during sleep [3, 14].

Genetic abnormalities

CPVT can be inherited either in an autosomal dominant (CPVT1) or recessive (CPVT2) way. The more common type 1 CPVT (MIM#604772) is caused by mutations in the cardiac ryanodine receptor gene *RyR2* on chromosome

Table 2 Symptoms and findings in catecholaminergic polymorphic ventricular tachycardia

Symptoms:

Exercise- or emotion-related syncope or sudden death

Cardiac imaging studies:

The structure of the heart is normal

Resting ECG:

Usually normal

The corrected QT interval <470 ms

Sinus bradycardia is possible

24-h Holter recording and exercise stress test:

The highly reproducible progressive worsening of arrhythmias during exercise consisting of PVCs, ventricular bigeminy, salvoes of polymorphic PVCs, polymorphic or bidirectional ventricular tachycardia

Atrial arrhythmias may precede ventricular arrhythmias during exercise

Electrophysiologic study:

Arrhythmias are seldom inducible by programmed electrical stimulation

Progressive ventricular arrhythmias may be induced in some cases by intravenous infusion of catecholamines

Gene defect:

RyR2 gene mutations

CASQ2 gene mutations

Other possible yet unknown gene defects

PVCs premature ventricular complex

Table 3 Inherited arrhythmogenic cardiac disorders causing malignant ventricular tachyarrhythmias

Disorder	Typical findings in the resting ECG	Clinical presentation
Catecholaminergic polymorphic ventricular tachycardia (CPVT)	Normal	Multifocal premature ventricular complexes and polymorphic ventricular tachycardia during exercise or emotional stress
Long QT syndrome (LQTS)	Prolongation of the QTc interval (>460 ms) Abnormal T-wave morphology	Arrhythmias associated with physical or emotional stress, sudden arousal or sleep
Brugada syndrome	ST elevation in the right precordial leads RBBB	Arrhythmias occurring at rest or during sleep
Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C)	T-wave inversion in the right precordial leads Epsilon waves	Arrhythmias during exercise LBBB pattern during tachycardia Structural abnormalities of the right ventricle
Short QT syndrome	Short QTc interval (<320 ms)	Very rare
Hypertrophic cardiomyopathy	LVH T-wave inversion	Outflow tract murmur due to hypertrophy of the left ventricle Syncope
Dilated cardiomyopathy	LVH Conduction disturbances	Cardiac insufficiency due to dilatation of the left ventricle

RBBB, right bundle branch block, *LBBB* left bundle branch block, *LVH* left ventricular hypertrophy

1q42-q43 and is a consequence of a defective calcium release from sarcoplasmic reticulum [8, 13, 19]. In the autosomal recessive variant, type 2 CPVT (MIM#611938), the causative gene, is the cardiac calsequestrin gene *CASQ2* located on chromosome 1p13-21 [6, 7]. *CASQ2* is a calcium buffering protein that has an active role in the control of calcium release from sarcoplasmic reticulum to cytosol. To date, there are over 70 known mutations in *RyR2* gene and seven known mutations in *CASQ2* gene associated with CPVT (more information is available online at <http://www.fsm.it/cardmoc/>). Mutations in the *RyR2* gene have been identified in around 50% and those in the *CASQ2* gene in <2% of patients with CPVT [5, 12]. Other yet unknown CPVT genes are likely to exist. In the study of Priori et al. [12], 90% of patients with non-genotyped CPVT were women and they became symptomatic in adulthood, at 20 (mean) $\pm$ 12 (SD) years of age, whereas the respective age was 8 (mean) $\pm$ 2 (SD) years in the *RyR2*-associated CPVT cases.

Therapy and prognosis

The cumulative mortality of the untreated CPVT cases is 30–50% by the age of 20–30 years [8, 9, 19]. Because of the poor prognosis of untreated CPVT, drug therapy is indicated for all clinically diagnosed patients and usually also for all silent carriers of a *RyR2* mutation [20]. According to the current knowledge, beta-antiadrenergic medication is the drug of choice [2, 9, 16], and a maximal

tolerated dose should be used. An implantable cardioverter-defibrillator is indicated for those patients who experience cardiac arrest, sustained VT or syncopal spell despite an adequate beta-blocker therapy [20]. Regular medication is of uttermost importance because missing even a single dose may lead to arrhythmias and increase the risk of sudden death [9]. Exercise stress test and Holter monitoring may help in finding the adequate dosage of the beta-antiadrenergic medication to control arrhythmias. It should be noted, though, that the absence of exercise-provoked arrhythmias does not completely exclude the risk of more severe arrhythmias. The aim of the medication is to avoid the heart rate exceeding the threshold heart rate for CPVT, and some studies have reported an almost complete prevention of cardiac events during beta-antiadrenergic medication [6, 11, 19]. However, other studies have reported a high recurrence rate of symptoms and even sudden death despite medication [2, 12, 16]. Calcium channel antagonists in combination with beta-antiadrenergic medication have been shown to significantly reduce the exercise-provoked ventricular arrhythmias in CPVT patients [18], but their impact in prognosis is not known.

Family report

A previously healthy 13-year-old boy fell unconscious whilst playing baseball at school. The onset was sudden,

not associated with any preceding symptoms but evidently associated with a short intensive running. Unconsciousness lasted about a minute, and some convulsive movements were observed in the legs. The boy recovered spontaneously and completely. There was no known preceding trauma, infection or intoxication. A few years earlier, the boy had experienced a near-drowning situation whilst swimming, but had managed to get up from the water. He had also felt occasional chest palpitations. In the emergency room, the patient was in good general condition. The clinical neurologic and cardiologic status was normal. The blood pressure was 116/70 mmHg, and the transcutaneous oxygen saturation was 98%. The basic laboratory tests as well as the chest X-ray and the electroencephalogram were all normal. The patient was monitored at an acute paediatric ward for 2 days, and no syncope, convulsions or arrhythmias occurred. The 12-lead ECG showed sinus rhythm with 56 bpm, and the corrected QT interval was normal (380 ms). The 24-h Holter recording revealed sinus rhythm between 40 and 113 bpm, and there were neither ectopic beats nor arrhythmias. The structure and the function of the heart were found to be normal on echocardiography.

The ECG during exercise stress test revealed multifocal PVCs when the sinus rate exceeded 130 bpm, followed by ventricular bigeminy and ventricular couplets (Fig. 1). After cessation of exercise, PVCs disappeared. Neither prolongation of the QT interval nor any ST-T changes were observed during the exercise stress test. The findings of the exercise ECG were diagnostic for CPVT. The magnetic resonance imaging of the heart confirmed the normal cardiac structures including the right ventricular outflow tract.

The family history indicated that the father of the patient had died suddenly in his 40s due to myocardial infarction, but there were no other known cases with heart disorders or sudden death. The patient's mother was on continuous medication for epilepsy. Her first syncopal episode had occurred at the age of 12 years, and the episodes appeared only during physical exercise or emotional stress. In the exercise ECG, the mother had over 400 multifocal PVCs starting at the heart rate of 118 bpm and a short ventricular tachycardia with four consecutive PVCs (Fig. 2). The 16-year-old sister of the patient had suffered from a few syncopal episodes, which were considered to be harmless vasovagal events. The exercise ECG of the sister revealed

Fig. 1 The chest lead electrocardiograms V1–V6 during exercise stress test of the index patient showing multifocal PVCs, bigeminy and a couplet

Fig. 2 The 12-lead ECG during exercise stress test of the mother of the index patient at workload 105 W, before beta-antiadrenergic medication, showing multifocal PVCs, bigeminy and couplets

Fig. 3 The chest lead electrocardiogram V2 during exercise stress test of the mother of the index patient at workload 105 W during beta-antiadrenergic medication. Indicator arrhythmias have not disappeared, but the heart rate has decreased showing a response to beta-antiadrenergic medication

over 160 predominantly single PVCs but also couplets, which started at a heart rate of 140 bpm. The antiepileptic medication of the mother was discontinued, and beta-blocker therapy was started both for the mother and the sister (Fig. 3).

The index patient was treated with a beta-blocker, bisoprolol, at a dosage of 0.2 mg kg⁻¹ day⁻¹. The aim of the medication was to prevent the heart rate from exceeding 130 bpm. The efficacy of beta-blocker therapy was confirmed by serial exercise stress tests and 24-h Holter recordings. In the Holter recordings, the mean heart rate stayed between 55 and 73 bpm also during physical activities. In the exercise stress tests, the maximal heart rate decreased from 184 bpm before medication to 122 bpm during medication, showing a good response to beta-blocker therapy. Competitive sports demanding vigorous physical exercise were prohibited. During a 2-year follow-up on medication, no syncopal episodes have occurred. Clustering of CPVT in the family suggests a dominant inheritance. The *RyR2* gene analysis is in progress

Conclusion

CPVT is an inherited cardiac arrhythmic disorder showing a malignant clinical course in the absence of structural defects in the heart. The mortality rate is high and a sudden death may occur in an otherwise healthy child or adolescent. The patients experience ventricular arrhythmias with modest exercise, emotional stress or exposure to catecholamines. In addition to the typical clinical picture, there are also reports of atypical CPVT cases with paroxysmal atrial fibrillation [10] or sudden deaths during sleep [1].

Diagnosing CPVT can be difficult especially in young children. When presumptive symptoms are encountered, an exercise ECG and Holter monitoring should be performed since CPVT cannot be diagnosed by a resting ECG or other cardiologic studies. Sometimes, the exercise-provoked arrhythmias can be demonstrated only after a delay of months or more after the first syncopal episode has occurred, emphasising the necessity of repeated exercise stress tests when there is a high suspicion of CPVT. In the case of a new CPVT diagnosis, it is essential to expand the evaluation to the rest of the family too to find other potential CPVT patients. Screening of family members by genetic testing is possible in the case of a known gene mutation. In most CPVT cases, symptoms can be prevented with beta-antiadrenergic medication. Drug treatment is indicated in all CPVT cases, including non-symptomatic patients diagnosed with a CPVT gene defect.

Conflict of interest There is no conflict of interest.

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