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CLINICAL CASE GALLERY REPORTS
Heart failure

Catecholaminergic polymorphic ventricular tachycardia complicated by dilated cardiomyopathy: a case report

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Background Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a severe genetic arrhythmogenic disorder characterized by adrenergically induced ventricular tachycardia manifesting as stress-induced syncope and sudden cardiac death. While CPVT is not associated with dilated cardiomyopathy (DCM) in most cases, the combination of both disease entities poses a major diagnostic and therapeutic challenge.

Case summary We present the case of a young woman with CPVT. The clinical course since childhood was characterized by repetitive episodes of exercise-induced ventricular arrhythmias and a brady-tachy syndrome due to rapid paroxysmal atrial fibrillation and sinus bradycardia. Medical treatment included propranolol and flecainide until echocardiography showed a dilated left ventricle with severely depressed ejection fraction when the patient was 32 years old. Cardiac magnetic resonance imaging revealed non-specific late gadolinium enhancement. Myocardial inflammation, however, was excluded by subsequent endomyocardial biopsy. Genetic analysis confirmed a mutation in the cardiac ryanodine receptor but no pathogenetic variant associated with DCM. Guideline-directed medical therapy for HFrEF was limited due to symptomatic hypotension. Over the next months, the patient developed progressive heart failure symptoms that were finally managed by heart transplantation.

Discussion Management in patients with CPVT and DCM is challenging, as Class I antiarrhythmic drugs are not recommended in structural heart disease and prophylactic internal cardioverter-defibrillator implantation without adjuvant antiarrhythmic therapy can be detrimental. Regular echocardiographic screening for DCM is recommendable in patients with CPVT. A multidisciplinary team of heart failure specialists, electrophysiologists, geneticists, and imaging specialists is needed to collaborate in the delivery of clinical care.

Keywords CPVT • Heart failure • Dilated cardiomyopathy • Case report

Learning points

- Even though catecholaminergic polymorphic ventricular tachycardia (CPVT) normally occurs in the absence of structural heart disease the clinical course can be complicated by dilated cardiomyopathy.
- To emphasize the need for a multidisciplinary diagnostic and therapeutic approach in patients with complex cardiac diseases.
- To highlight the importance of regular echocardiographic screening in patients with CPVT.
- To point out the difficulties in the management of a patient with both CPVT and heart failure with reduced ejection fraction.

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Background

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by the induction of polymorphic ventricular arrhythmias in response to adrenergic stress. Mutations in the Ryanodine receptor gene (RyR2—dominant form) or in the Calsequestrin 2 gene (CASQ2—recessive form) are associated with CPVT.[1] Both receptors are located in the sarcoplasmic reticulum and are involved in intracellular calcium handling and homeostasis.[1] Despite the early onset of the disease (most patients experience stress-induced syncope or cardiac arrest already in their childhood), diagnosis is often delayed. This can be explained by a normal resting electrocardiogram (ECG) as well as the absence of structural cardiac abnormalities.[1,2] Catecholaminergic polymorphic ventricular tachycardia can be unmasked by a treadmill stress test inducing ventricular ectopy. Additionally, a history of sudden cardiac death or stress-induced syncope in first-degree family members is a frequent finding.[1,2] The diagnosis of CPVT can be confirmed by genetic testing.[1,2] As alternative diagnoses, long QT syndrome, arrhythmogenic right ventricular (RV) cardiomyopathy, and Andersen–Tawil syndrome must be considered.[2]Beta-blockers (nadolol and propranolol) still represent the most relevant therapeutic option. In patients with insufficient arrhythmia suppression, sodium channel blockers such as flecainide can be added.[2] Patients are counselled to avoid strenuous exercise or competitive sports to prevent arrhythmogenic events.[1,2]

Timeline

Year	Event
1990	Diagnosis of catecholaminergic polymorphic ventricular tachycardia, start of propranolol
2007	Cardiac magnetic resonance imaging (MRI) and echocardiography without relevant structural or functional pathology
2016	Routine echocardiography—severely reduced left ventricular ejection fraction and dilated left ventricle
2016	Guideline-directed medical therapy for heart failure with reduced ejection fraction (HFrEF) is initiated
2016	Diagnostic workup: cardiac MRI, endomyocardial biopsy, left heart catheterization, genetic analysis
2016–2017	Aetiology of heart failure remains elusive, progressive heart failure symptoms
2017	Successful heart transplantation

Patient presentation

We present the case of a 36-year-old woman with a long-standing genetically confirmed diagnosis of CPVT. The diagnosis was established at the age of six (in 1990) when she suffered a syncopal episode during a sports event. Anticonvulsive therapy was started initially for a suspected epileptic seizure. Further cardiologic testing was prompted by the patient's history of palpitations precipitated by emotional or physical stress that was associated with dyspnoea and occasional vertigo. Electrocardiography demonstrated a normal QT interval and frequent premature atrial and ventricular contractions. During exercise testing, a bidirectional ventricular tachycardia (VT) at a rate of 160 b.p.m. was observed (*Figure 1*). Genetic testing revealed CPVT. Her family history was unremarkable for sudden cardiac death; family screening for CPVT was negative. She was started on propranolol (30–40–40 mg) and counselled to avoid competitive sports and strenuous exercise. Flecainide (50 mg bid) was added on top of propranolol in 2012 for further arrhythmia suppression. Apart from the complex ventricular arrhythmias, frequent episodes of paroxysmal rapid atrial fibrillation manifested as brady-tachy syndrome. Repeated echocardiography and a cardiac magnetic resonance imaging (MRI) in 2007 revealed no relevant structural or functional pathology. Regular clinical follow-ups with Holter ECG were conducted in the arrhythmia outpatient clinic. Symptoms including palpitations and lightheadedness improved significantly since the introduction of flecainide. Simultaneously, the dosage of propranolol had to be reduced as symptomatic sinus bradycardia and sinus arrests up to 4 s were documented on Holter ECG. Following a flu-like illness (in 2015), event recording revealed ventricular bigeminy, paroxysmal atrial fibrillation, and sinus bradycardia (34 b.p.m.) resulting in episodes of dizziness.

In 2016, our patient was referred to the heart failure outpatient clinic for routine echocardiography. She presented in good general health without acute distress, height 158 cm, weight 54 kg, blood pressure 106/63 mmHg. In the clinical exam, no peripheral oedema or jugular venous distension was evident. Cardiac auscultation revealed a holosystolic murmur with punctum maximum at the apex while pulmonary auscultation remained without any abnormalities. Laboratory results showed a significant elevation of N-terminal prohormone of brain natriuretic peptide levels (5648 pg/mL) without any other relevant abnormalities. Transthoracic echocardiography showed a dilated left ventricle and a severely depressed left ventricular (LV) function without regional wall motion abnormalities. Further findings included RV dilatation and moderate to severe functional mitral regurgitation (*Figure 2A and B*).

Initial workup

As a consequence of these findings, the patient was admitted to our inpatient clinic and underwent an extensive diagnostic workup to determine the underlying cause of *de novo* cardiomyopathy.[3] Cardiac MRI showed a severely depressed left ventricular ejection fraction (LVEF) and marked biventricular dilatation [LVEF: 18%, LV end diastolic volume (EDV): 179 mL, LV end systolic volume (ESV): 147 mL, cardiac index (CI): 1.1 L/min/m^2]. Post-gadolinium studies revealed a patchy subepicardial and transmural late enhancement. T2 relaxation time was within normal limits excluding acute oedema. T1 mapping and extracellular volume (ECV) for quantification of diffuse myocardial fibrosis were not available (*Figure 3A–C*). Endomyocardial biopsy revealed no signs of

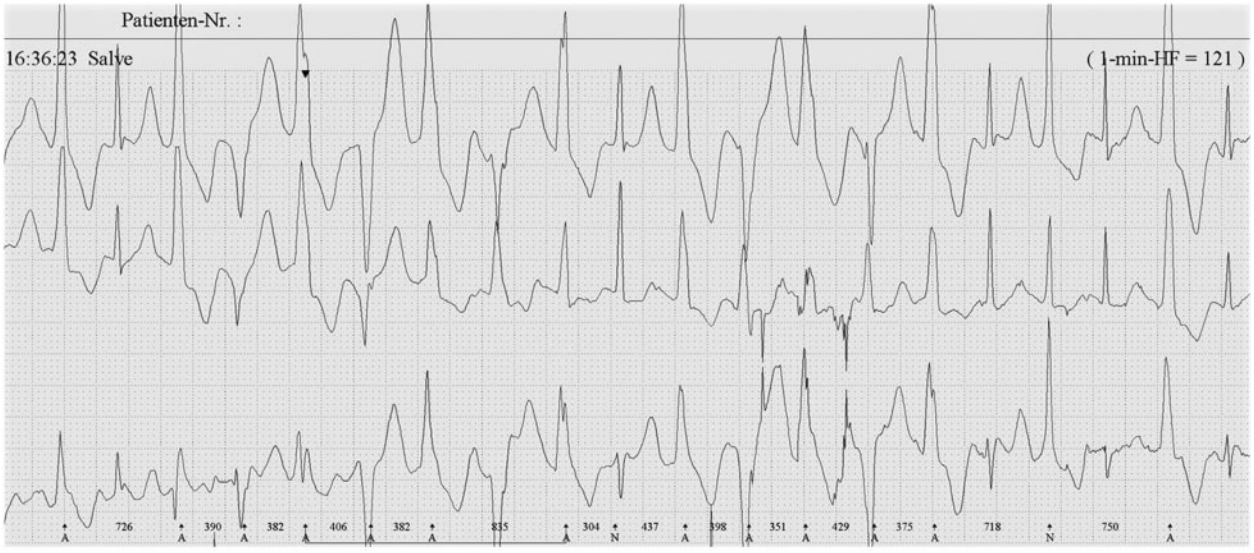

Figure 1 Bidirectional ventricular tachycardia can occur in patients with catecholaminergic polymorphic ventricular tachycardia and is considered to result from intracellular calcium overload leading to delayed afterdepolarizations causing triggered activity. The delayed afterdepolarizations induce epicardial extrasystoles by increasing transmural dispersion of depolarization. This creates the substrate for reentry-based rapid polymorphic ventricular tachycardia. Biventricular tachycardia is caused by alternating epicardial/endocardial beats. The hallmark of this form of ventricular tachycardia is a fast but regular rhythm with a different axis of every other beat.

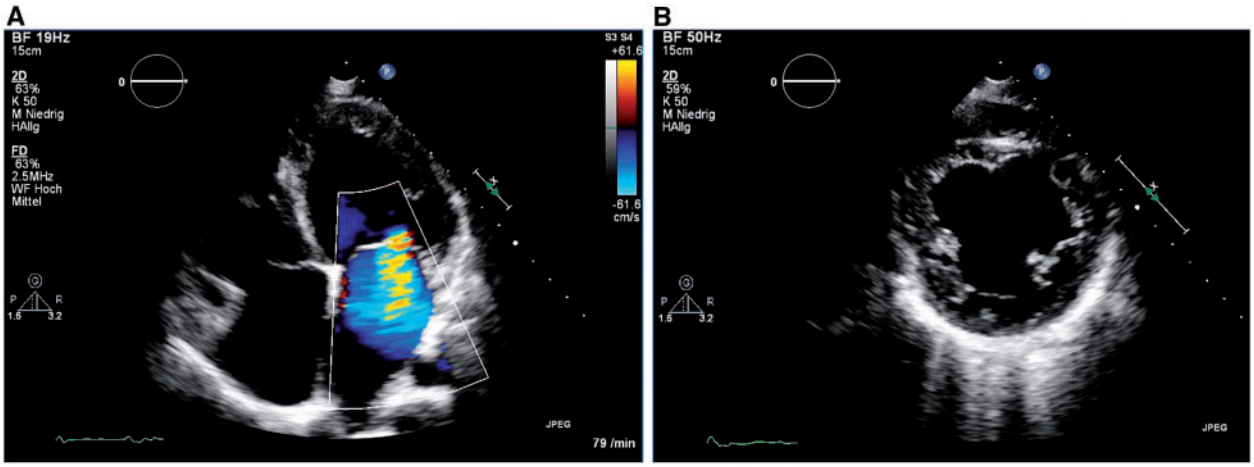

Figure 2 Transthoracic echocardiography showing left ventricular dilatation and moderate to severe functional mitral regurgitation. (*A*) Four-chamber view and (*B*) parasternal short-axis view.

myocarditis. Masson trichrome staining revealed hypertrophic and degenerated myocytes and interstitial fibrosis, typical for dilated cardiomyopathy (DCM). No inflammatory infiltration was found in immunohistochemical staining, as exemplary shown for CD3 T-cell staining. Nested polymerase chain reaction (PCR) revealed a low-level myocardial parvovirus B19 persistence, which was not regarded as significant (*Figure 4A and B*). Left heart catheterization excluded the presence of coronary artery disease. Genetic analysis was repeated because the original report of genetic testing in childhood was not available anymore and because of the atypical phenotypic features for CPVT. Next-generation sequencing disclosed a pathogenic mutation in the cardiac ryanodine receptor 2 gene (c.12006G>A, p. Met4002Ile), but did not identify a pathogenic gene variant typically associated with DCM.

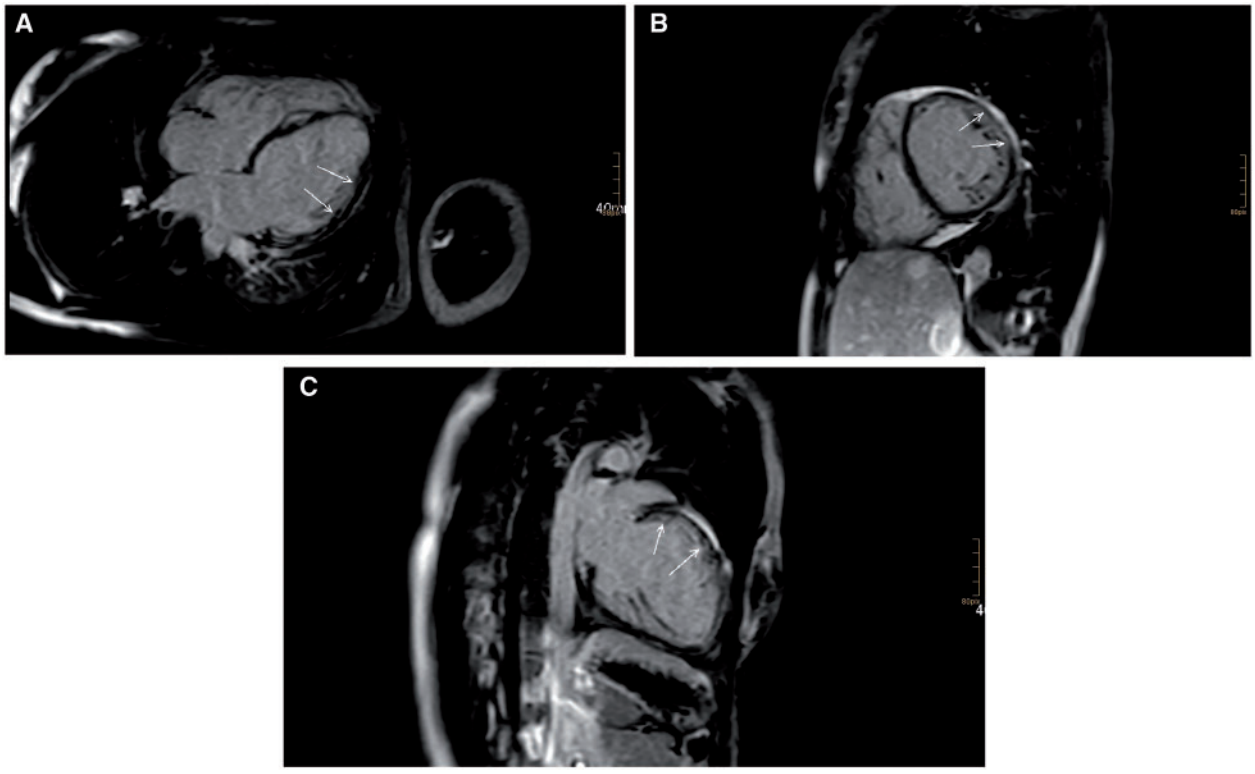

Figure 3 Late gadolinium enhancement in (*A*) four-chamber view, (*B*) short-axis view, and (*C*) two-chamber view: thinned left ventricular myocardium with subendocardial late enhancement along the lateral and anterior wall of the left ventricle (arrows).

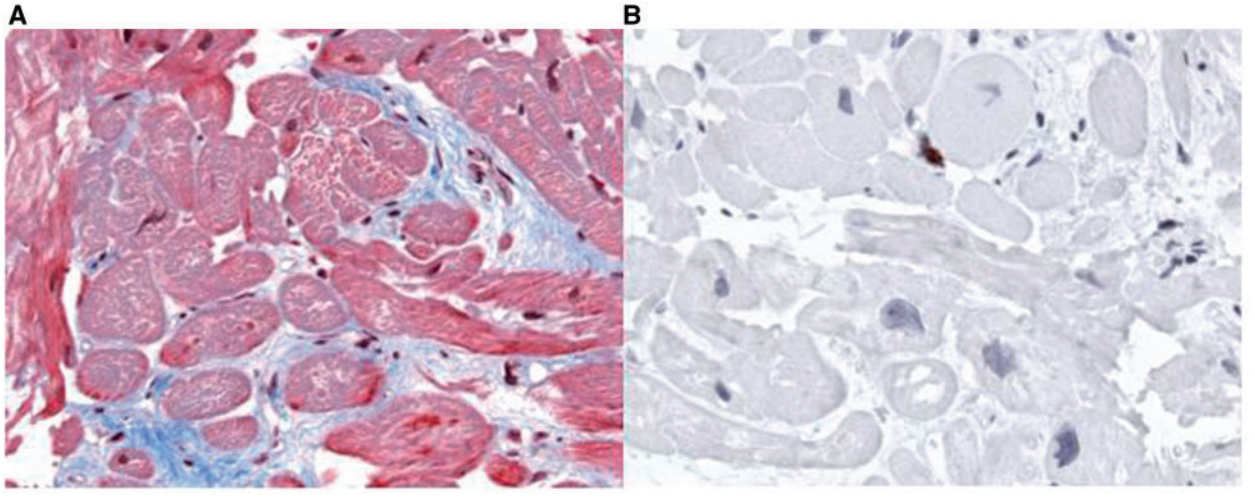

Figure 4 Endomyocardial biopsy. (*A*) Masson trichrome staining reveals hypertrophic, degenerated myocytes, and interstitial fibrosis, typical for dilated cardiomyopathy. (*B*) No inflammation is found in immunohistochemical stainings, as exemplarily shown for CD3 T-cell staining.

Disease course

As Class I antiarrhythmic drugs are not recommended in patients with structural heart disease, the sodium channel blocker flecainide was reduced to 25 mg bid.[3] Holter ECG monitoring demonstrated a brady-tachy syndrome with functional sinus bradycardia (<30 b.p.m.) due to blocked atrial bigeminy, atrial tachycardia, atrial fibrillation, pauses of 3.3 s and non-sustained

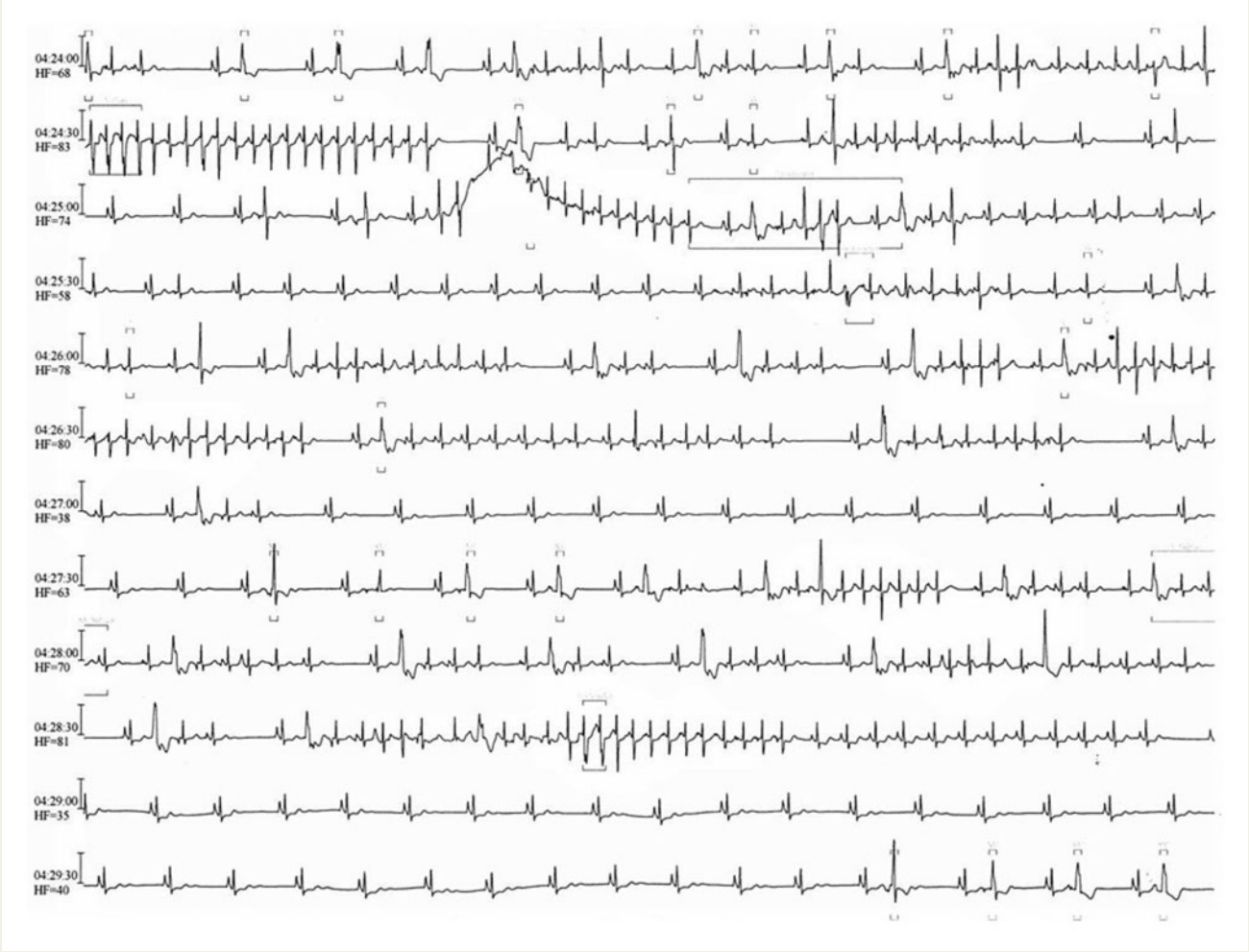

Figure 5 Holter electrocardiogram showing blocked atrial bigeminy, atrial tachycardia, and non-sustained monomorphic ventricular tachycardia.

monomorphic VT at a CI 340 ms (*Figure 5*). Internal cardioverter-defibrillator (ICD) implantation for primary prevention had been considered repeatedly throughout the course of the disease. After extensive discussion, the patient and her parents declined an ICD even at this stage of disease progression.[4]Guideline-directed medical therapy for HFrEF was limited due to symptomatic hypotension. Over the next few months, the patient developed rapid progression of heart failure with increasing dyspnoea on exertion and fluid overload and ultimately required hospitalization for acute decompensated heart failure. Right heart catheterization demonstrated severely decreased cardiac output with a CI of 1.7 L/min/m^2 and postcapillary pulmonary hypertension [systolic pulmonary artery pressure (sPAP) 50 mmHg, mean pulmonary artery pressure (mPAP) 31 mmHg, pulmonary capillary wedge pressure 21 mmHg, pulmonary vascular resistance (PVR) 4.2 WU]. Because of rapid disease progression including heart failure symptoms and electrical instability, the patient was finally listed for cardiac transplantation. She was successfully transplanted in 2017 and continues to do well since then.

Discussion

In our patient, despite an extensive diagnostic workup, the aetiology of heart failure remained elusive. While a correlation between disturbances in calcium handling and the initiation and progression of heart failure is reported in the literature, no evidence exists for an association of RyR2 and CASQ2 mutations with DCM.[5,6] A possible history of myocarditis, tachycardiomyopathy due to severe and persistent arrhythmias and DCM were considered as differential diagnoses.[3] On top of the hereditary arrhythmogenic syndrome, an additional risk for sudden cardiac death was present due to symptomatic HFrEF (LVEF < 35%). In CPVT, however, ICDs are primarily recommended in patients with episodes of cardiac arrest, recurrent syncope, or polymorphic/bidirectional VT despite optimal therapy, as the device therapy is associated with a high burden of shocks and complications. Although the ICD intuitively seems to be a logical option in the management of a potentially lethal cardiac condition, nuances that are unique to CPVT make the utilization controversial. It has to be considered that painful, adrenaline-provoking shocks are potentially pro-

arrhythmic in CPVT, that complex atrial and ventricular arrhythmias may trigger inappropriate shocks, and that the typically young age of CPVT onset accentuates the lifetime risk of device complications, such as infections and lead failure.

Conclusion

Catecholaminergic polymorphic ventricular tachycardia is a severe genetic arrhythmogenic disorder characterized by adrenergically induced VT manifesting as stress-induced syncope and sudden cardiac death. In most cases CPVT is not associated with DCM. Management in patients with CPVT who develop DCM is challenging, as Class I antiarrhythmic drugs are not recommended in structural heart disease and prophylactic ICD implantation without adjuvant antiarrhythmic therapy can be detrimental. Regular echocardiographic screening for DCM is recommendable in patients with CPVT. A multidisciplinary team of heart failure specialists, electrophysiologists, geneticists, and imaging specialists is needed to collaborate in the delivery of clinical care.

Questions

Question 1: What is the correct diagnosis of the arrhythmia shown on the monitor strip (*Figure 1*)?

(1) Torsades de pointes.
(2) *Bidirectional ventricular tachycardia.*
(3) Multifocal ventricular premature beats.
(4) Pre-excited atrial fibrillation.

Question 2: What is shown on the following echo-loops (*Figure 2*)?

(1) Moderate to severe functional mitral regurgitation.
(2) Biventricular dilatation.
(3) Severely depressed LV function.
(4) *All of the above.*

Question 3: Which of the findings below is not typical for CPVT?

(1) Syncope or cardiac arrest in the childhood.
(2) Structurally normal heart.
(3) Normal baseline electrocardiogram.
(4) *Dilated cardiomyopathy (DCM).*

Question 4: Which statement regarding genetic testing is not correct according to the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure?

(1) DCM is idiopathic in 50% of cases, about one-third of which are hereditary.
(2) The most frequent genes associated with DCM are titin (TTN), lamin (LMNA), and desmin (DES).
(3) *In most patients with a definite clinical diagnosis of HF, there is a confirmatory role for routine genetic testing to establish the diagnosis.*
(4) Lamin and phospholamban mutations are related to a poorer prognosis.

Question 5: According to the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, ICD implantation is not recommended. . .

(1) In patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status.
(2) In patients with symptomatic heart failure (NYHA Class II–III) and an LVEF ≤35% despite ≥3 months of optimal medical therapy.
(3) *In patients who had a myocardial infarction in the prior 40 days.*

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Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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