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Case report

Dizziness and syncope in young people: keep your mind open! Case report and literature review of the challenging differentiation between arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) and catecholaminergic polymorphic ventricular tachycardia (CPVT).

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Abstract. This article describes a paradigmatic case of aborted sudden cardiac death (SCD) in a young man, reflecting the challenge of diagnosing a variety of conditions that potentially underly this dramatic disorder. Based on the clinical characteristics of this case, presenting some overlapping clinical features common to both the diseases, the discussion will be focused on Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D). The epidemiological, genetic, diagnostic and therapeutic aspects are also discussed. (www.actabiomedica.it)

Key words: Catecholaminergic Polymorphic Ventricular Tachycardia; CPVT; Arrhythmogenic right ventricular cardiomyopathy/dysplasia; ARVC/D; Channelopathy; Syncope; Sudden Cardiac Death.

Case report

A 27-years old male was referred to the Emergency Department (ED) of the Academic Hospital of Parma, on January 16th 2013, by ambulance emergency services. During a cross-country skiing race, after approx 30 min from the start, he suddenly felt dizzy and suddenly crashed down, unconscious. He then became spontaneously conscious in a few seconds, before some witnesses could establish cardiopulmonary resuscitation (CPR). The first electrocardiogram (ECG) at ED arrival showed slight sinus bradycardia and T-wave inversion in leads V4-V6, but no epsilon waves were found (Figure 1). During clinical management in the ED, the patient suddenly felt again dizzy but without losing consciousness because he was lying on a bed. A new ECG was immediately obtained, which showed a wide-complex tachycardia, strongly suggestive for Ventricular Tachycardia (VT) (Figure 2). The patient was immediately shocked (sedation with fentanyl 1 μg/Kg, and midazolam 0.3 mg/Kg, followed by biphasic DC shock, 200 J), with immediate restoration of normal sinus rhythm. Hereafter the sinus rhythm was maintained, and the patient did not complain for other symptoms. The patient has been previously well until this episode, and had never lost consciousness before, although he referred to have suffered from some palpitations episodes over the past years, mainly occurring during physical efforts. Exercise testing (i.e., treadmill ECG test) was non diagnostic, showing only some isolated premature ventricular beats (PVB). Echocardiography did not reveal any morphologic or

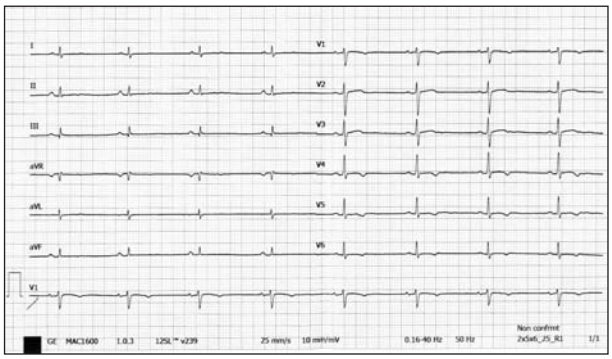

Figure 1. The electrocardiogram of the patient obtained during the initial ED evaluation.

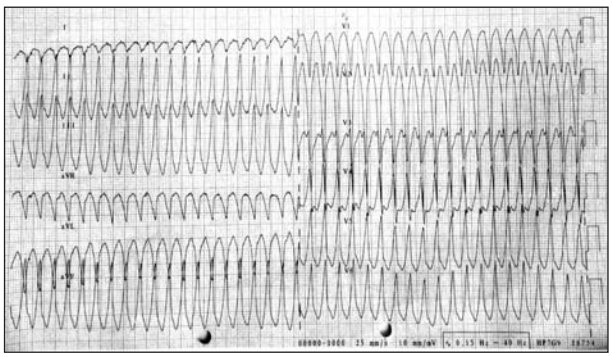

Figure 2. The electrocardiogram of the patient obtained during the "dizziness" episode occurring during his staying in the ED.

dynamic alteration. The patient was hence referred to the Cardiology Unit for electrophysiologic study under cathecolamine infusion, which demonstrated inducibility of ventricular tachycardia, and finally raised the suspicion of catecholaminergic polymorphic ventricular tachycardia (CPVT). Endomyocardial biopsy did not reveal any pathological aspect. Based on these findings, the patient was given beta-blockers. About 2 months later, the patient underwent a cardiac magnetic resonance (CMR), which was positive, based on major criteria, for Arrhythmogenic Cardiomyopathy/Dysplasia, involving both right and left ventricles. The genetic analysis of the patient, that was only possible some months later, did not reveal any mutation or polymorphism compatible with CPVT. The patient was then implanted with an ICD, and is now in a good shape.

Introduction

It is estimated that more than 7 million lives per year are lost due to sudden cardiac death (SCD) worldwide (1). Most cases (i.e., ~80%) are attributed to underlying coronary artery disease (CAD), but a non negligible 5-10% of all cases occur in young, apparently healthy individuals. Those cases are classified as sudden arrhythmic death syndrome (SADS). According to international reports, 30% of families of SADS victims were found to have a potentially inherited cardiac disease. Among the causes of SADS in young people, the best known include Brugada syndrome (BS), long QT syndrome (LQTS), short QT syndrome (SQTS), pre-excitation syndromes, such as Wolf-Parkinson-White (WPW) syndrome, and arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).

Overview on catecholaminergic polymorphic ventricular tachycardia (CPVT)

CPVT has been more in depth studied and genetically characterized only in the past few years. Like most of the aforementioned diseases, this condition belongs to a family of genetic disorders known as "channelopathies" (2-5). CPVT is an inherited arrhythmia syndrome characterized by bidirectional or polymorphic ventricular arrhythmias, possibly exiting in SCD, and often triggered by conditions of increased sympathetic activity in young subjects with structurally normal hearts. When left untreated, patients with CPVT have a high risk of developing life-threatening ventricular arrhythmias, which are actually one of the most malignant forms of ventricular arrhythmia (6,7). CPVT appears to result from a defect of intracellular calcium cycling that triggers transient inward current. Missense mutations underlying CPVT have been identified in 2 genes, i.e., ryanodine receptor 2 (RyR2) and calsequestrin 2 (CASQ2) (8). CPVT syndrome is also known with the following synonyms: Familial Polymorphic Ventricular Tachycardia, CASQ2-Related Catecholaminergic Ventricular Tachycardia, RYR2-Related Catecholaminergic Ventricular Tachycardia (9).

The underlying mechanisms and origin of bidirectional tachycardia have been debated since this condition was first described by Schwensen in 1922 (10), although the familiar nature of CPVT was only elucidated in the early '60s, when the cases of three sisters with syncope and polymorphic ventricular arrhythmias in the absence of structural heart disease were described (11). Later on, in 1978 and 1995, Coumel et al. and Leenhardt et al. reported a series of cases of the arrhythmia, both in familial and in sporadic forms, and introduced the term "catecholaminergic polymorphic ventricular tachycardia" to define a disease characterized by adrenergically mediated ventricular tachycardia in the lack of cardiac structural pathology (7,12). Our understanding of genetic basis of this disease began with a report by Swan et al. at the end of the past century, who described two unrelated Finnish families with a typical presentation of CPVT, segregating in an autosomal-dominant mode, and with a disease locus on chromosome 1q42-q43 (13). Priori et al., and shortly afterwards Laitinen et al., identified mutations in the cardiac ryanodine receptor gene (RyR2) in families suffering from one type of CPVT, now conventionally known as CPVT1, which recognizes an autosomal dominant pattern (14,15). A recessive form of disease, with a missense mutation in a highly conserved region of the cardiac calsequestrin gene (CASQ2), has been described by Lahat et al. in seven nuclear families belonging to a Bedouin tribe from the north of Israel with a history typical of CPVT, now termed CPVT2. The gene has been mapped on chromosome 1p13-21 (16,17). RYR2, which encodes for ryanodine receptor, is a critical component of calcium homeostasis and associated excitation–contraction coupling in the myocardiocyte, whereas CASQ2 encodes for cardiac calsequestrin, a protein located within the sarcoplasmic reticulum, which also plays a pivotal role in intracellular calcium homeostasis (18,19). Compared with RyR2-linked CPVT1, which accounts for 50% of CPVT cases, Casq2-linked CPVT2 is by far less common (2%), but often more clinically severe. Accurate data on the prevalence of de novo mutations are unavailable, but estimated to approx 40% (20).

CPVT classically presents with syncope, severe dizziness, aborted cardiac arrest (ACA) or SCD, usually associated with exercise or intense emotional stress. The first symptoms usually appear in the first or second decade of life, and may often be misclassified as epilepsy in children. (19). Some cases of sudden infant death syndrome (SIDS) have also been associated with mutations in RYR2 (21). The prevalence of CPVT in the general population has not been definitely established, but it is estimated around 1:10,000, with an overall mortality rate up to 50%, when left untreated. Approximately one-third of affected individuals experiences at least one cardiac arrest, and up 80% one or more syncopal events. From a clinical standpoint, a history of syncope during exercise or sympathetic activation are the leading aspects that raise suspicion of this disease. Unfortunately, the 12 lead rest ECG does not often reveal any relevant abnormality. Sometimes, CPVT patients may be bradycardic, but this finding is not unusual in healthy, athletic, young subjects. Cardiac imaging does not actually show substantial structural problems, and the lack of abnormalities is often considered a landmark for diagnosing CPVT. The gold standard for the diagnosis is indeed exercise testing, either by treadmill or bicycle ergometer. The heart rate threshold of the first isolated ventricular premature beat (VPB) is typically reproducible in single individual patients, and is usually comprised between 110 and 130 beats per minute. Holter monitoring should be reserved to those patients who are unable to perform an adequate exercise test, or in patients suspected of having emotion-related rather than exercise-related VT. Overall, the sensitivity of Holter monitoring to detect VT in CPVT patients is much lower than that of exercise testing. Electrophysiology studies can usually trigger VT by adrenergic stimulation (i.e., infusion of catecholamines) (19). The risk stratification for occurrence of arrhythmic events in CPVT patients has been poorly defined so far. At variance with other inherited channelopathies such as Brugada syndrome and LQTS, there are no reliable tools to identify CPVT patients at low risk of arrhythmic events, in whom the treatment could be safely withheld. As such, all clinically or genetically diagnosed CPVT patients should be actively treated (22,23).

Each newly diagnosed CPVT patient should first be counseled on the consequences of this disease.

Since either physical or emotional exertion can trigger ventricular tachycardia, the "*Recommendations for Physical Activity and Recreational Sports Participation for Young Patients With Genetic Cardiovascular Diseases*" published by the American Heart Association (AHA) in 2004, state that patients "*should be cautioned against virtually all forms of vigorous physical activity*", although no further detailed information is provided (24). β-blockers are currently considered the milestones of drug therapy in CPVT (Class I, level of evidence C, according to the available guidelines) (25,26), since they are effective to dramatically reduce the risk of arrhythmic events (24,27). Patients should receive the highest tolerable β-blocker dose. A growing evidence suggests that flecainide, when added to β-blocker treatment, is the most effective additional therapeutic approach (6,28). Left cardiac sympathetic denervation may be advisable in patients who cannot be controlled by multiple drugs treatment (29,30). ICD therapy may be reserved to those patients who display arrhythmic events despite maximal drug treatment (Class I, level of evidence C, according to the available guidelines). This last recommendation is based on the fact that several case reports have shown that ICDs may be proarrhythmic in CPVT, because appropriate or inappropriate ICD shocks may be associated with a subsequent catecholamine release, that may trigger arrhythmic storms, potentially leading to death (25) .

Overview on arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)

Although ARVC/D is a form of cardiomyopathy that primarily affects the right ventricle (RV), it may also involve the left ventricle (LV) and culminate in life-threatening ventricular arrhythmias, possibly exiting in SCD, and/or heart failure.

The very first description of ARVC/D can be attributed to the Pope's physician, Giovanni Maria Lancisi who, in his book entitled "*De Motu Cordis et Aneurismatibus…*" and published in 1728 (31), reported the case of a family which experienced juvenile heart failure and SCD in four consecutive generations. The first comprehensive clinical description of the disease can be attributed to Marcus et al. in 1982, who reported 24 adult cases of ventricular tachyarrhythmias with left bundle branch morphology (32). Nevertheless, it was not until the 1984 that the ECG features of disease were first described, including the epsilon wave (33).

ARVC/D is characterized by myocardial atrophy, fibrofatty replacement, fibrosis and ultimate thinning of the wall, with chamber dilation and aneurysm formation (34). These changes consequently trigger electrical instability, which may precipitate VT, VF and SCD (35,36). The estimated prevalence of ARVC/D in the general population is approximately 1:5000, with a 3:1 male to female ratio (37). ARVC/D accounts for 11-22% of SCD cases in the young athlete patient population (38). Therefore, it accounts for approximately 22% of cases in athletes in northern Italy (39), and about 17% of SCD in young people in the United States (40).

ARVC/D was initially considered as secondary to a developmental defect of the RV myocardium, leading to the original designation of "dysplasia". Nevertheless, this notion has evolved over the last 30 years. Based on its clinical characteristics, pathophysiology, post-natal development and genetic background, its inclusion in the World Health Organization (WHO) classification of cardiomyopathies has been finally achieved (41), despite there are still controversial evidence on this issue. Different pathogenetic mechanisms have been postulated, involving congenital defects, genetics and acquired factors. This hypothesis has evolved into the idea of genetically determined cardiomyopathy, which is transmitted with an autosomal dominant pattern of inheritance, with incomplete penetrance and variable expression in approx 30-50% of cases (42). Acquired factors have also been hypothesized as potential causes of ARVC/D, with the strongest association found for viral myocarditis. On histopathology, a lymphocytic infiltrate with disappearance of myocytes and fibrofatty replacement is often detected, a characteristic pattern that can also be observed in viral myocarditis (43). It is hence plausible to put forward the hypothesis that the wide variation of ARVC/D presentation may be explained by its genetic heterogeneity and the presence of modifying factors such as exercise and/or viral myocarditis (44).

Nearly 90% of ARVC/D patients display some ECG abnormalities. One of the most common presentations is prolonged S-wave upstroke >55 ms in V1-V3

(in up to 95% of cases), followed by an inverted T wave on precordial leads (V1-V3), which occurs in half of cases presenting with VT. Inverted T waves (repolarization abnormality) are included in the 2010 Revised Task Force Criteria and represent a major criterion in the absence of complete RBBB (45). QRS prolongation (QRS >110 msec), particularly in lead V1, has been observed in 24-70% of patients with ARVC/D (46). An epsilon wave (depolarization abnormality) may be found in 30-33% of patients with ARVC/D (47), which is described as a distinct wave at the end of QRS complex, probably secondary to slowed intraventricular conduction (Figure 3). CMR is widely used for diagnosis of ARVC/D and allows to identify global or regional ventricular dilation, dysfunction, intramyocardial fat, aneurysmatic dilation and fibrosis. According to the proposed 2010 diagnostic criteria, an enlarged RV is no longer sufficient, because it may be observed in other infiltrative disorders such as sarcoidosis, amyloidosis, congenital heart diseases and pulmonary hypertension. Therefore, the diagnostic criteria now require the presence of akinesia, dyskinesia or aneurysm in addition to a decreased RV ejection fraction or increased RV end diastolic volume to body surface area ratio.

Clinical diagnosis of ARVC/D is often difficult due to the non-specific nature of the disease and the broad spectrum of phenotypic variations. There is no definitive diagnostic gold standard. Positive result of endomyocardial biopsy (EMB) of RV is the mostly used approach for diagnosis, but this analysis often produces false-negative results and the assessment of transmural myocardium is impossible in most patients due to the fact that the disease spreads from epicardium to endocardium. The sensitivity of EMB is approximately 67% because of the regional fibroadipose infiltration (48). Consequently, the best approach in making a diagnosis of ARVC/D is the combination of different diagnostic tests.

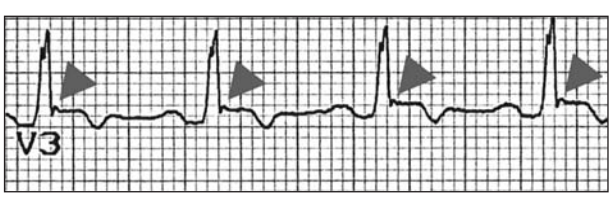

Figure 3. The epsilon wave (red arrows). Freely available from the web.

As regards the therapeutic approach, early intervention with an Implantable Cardioverter-Defibrillator (ICD) decreases the risk of SCD, but ARVC/D is a progressive disease, which can progress to refractory VT or a ventricular fibrillation (VF) storm despite ICD implantation.

The indications of ICD for primary prevention of SCD in ARVC/D patients have not been definitely established (49,50). There is a general consensus that high-risk patients should be considered as candidates to ICD placement. Consequently, patients with episodes of sustained VT or VF (Level of Recommendation: IB), unexplained syncope, non-sustained VT on noninvasive monitoring, familial history of sudden death, extensive disease including those with LV involvement and good functional status (Level of Recommendation: IIaC) (49,50) are potential candidates for ICD implantation even in the absence of ventricular arrhythmias (51).

Discussion and conclusions

In the differential diagnosis of idiopathic VTs, some other conditions should be weighted, such as right ventricle outflow tract VT, left ventricle outflow tract VT, idiopathic left ventricular tachycardia, catecholaminergic polymorphic VT (CPVT), Brugada syndrome, long QT Syndrome and short QT syndrome (19,27,52).

Right ventricular outflow tract tachycardia (RVOT) and CPVT are the leading differential diagnoses of ARVC/D. The presentation and ECG characteristics of VT may be rather similar in these conditions (VT with LBBB but with an inferior axis). However, RVOT tachycardia is considered as a primary electrical condition in the absence of structural heart disease, and CPVT is recognized as a channellopathy, unlike ARVC/D. Epidemiologically, RVOT tachycardia is more common than ARVC/D, whereas CPVT is very rare.

Recently, a high degree of association between PVCs at baseline and the VTs induced during catecholamine infusion has been reported in ARVD/C patients (53). These VTs originate from the border re-

gion of scar, most commonly in the right ventricular outflow tract and right ventricle basal regions. These findings highlight the importance of catecholamine challenge and PVC mapping, in order to support the differential diagnosis with CPVT and facilitate ablation of the VT, whenever possible, in arrhythmogenic right ventricular dysplasia/cardiomyopathy.

Surprisingly, recently some mutations in RYR2 have also been identified in patients with fibro-fatty myocardial replacement in the right ventricle, thus similar to arrhythmogenic cardiomyopathy (54). This represents a further challenge in the classification and diagnostics of these conditions.

Our paradigmatic case mirrors the challenge of diagnosing the various conditions discussed in this article, and this is mainly due to some overlapping clinical features, and the natural evolution of the disease, that is seldom recognized only after months/years from the clinical presentation.

The pursuit of a greater knowledge on the genetic basis of SCD is necessary for achieving a substantial improvement of management of genetic SCD syndromes, development of novel therapeutics, and risk stratification in the general population, thus improving our ability to predict and ultimately prevent severe clinical outcomes, up to death. We can hence conclude that the Emergency Physician should clearly recognize the heavy implications of symptoms like dizziness and syncope, even in the young, apparently healthy, patients. When the clinical suspicion is high, consultation with expert arrhythmologists and referral to specialized centers seems to be the mainstay for saving the lives of patients with some of these life-threatening conditions.

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