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Case Report

Catecholaminergic polymorphic ventricular tachycardia in adolescents: A clinical, electrocardiographic and genetic diagnosis

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ABSTRACT

Catecholaminergic polymorphic ventricular tachycardia is one of the most lethal channelopathies, characterized by ventricular arrhythmias triggered by stress or physical activity. We present the case of an adolescent who consulted for recurrent syncope precipitated by exercise. In the diagnostic approach, catecholaminergic polymorphic ventricular tachycardia was reached, with a mutation in the cardiac ryanodine receptor gene, Heterozygous c.14311G> A (p.v4771I exon 100), antiarrhythmic drugs and implantable cardioverter-defibrillator were necessary with satisfactory evolution. Clinical suspicion, stress test and genetic tests are essential for a timely diagnosis and management of this pathology.

Keywords: Tachycardia, ventricular; Syncope; Death, sudden; Genetic; Ryanodine (source: MeSH NLM).

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inheritable channelopathy, characterized by the appearance of monomorphic ventricular complexes, progressing to bidirectional and/or polymorphic ventricular tachycardia during physical exertion, emotional stress, or during infusion of catecholamines in structurally intact hearts, without alterations in the baseline electrocardiogram (ECG). The estimated prevalence of CPVT is 1 per 10 000 individuals, and about 30% of patients have a family history of sudden cardiac death [1,2].

Clinical manifestations generally begin at 6 - 10 years of age [2], and the most common are recurrent syncope (80%) triggered during physical activity, cardiorespiratory arrest (30%), and in the worst cases, sudden death, which in children and adolescents is uncommon, although in untreated young adults it has been reported in 30% of cases [3,4].

Recent research has categorized multiple causes of CPVT: 1) CPVT with mutations or juvenile: approximately 55% of patients have mutations in the RyR2 gene, cardiac ryanodine receptor type 2; located on the long arm of chromosome 1 (1q43), with an autosomal dominant pattern of inheritance [5]. Mutations in the cardiac calsequestrin-2 gene CASQ2 (1p13.1) with an autosomal recessive pattern present in 2% of cases [2]. Other mutations have also been described with a lower incidence in the triandin, trianin, and adenylate kinase-2 genes (5); 2) sporadic or non-genotyped CPVT accounts for 39% of cases, mainly affecting women over 20 years of age [5], and 3) CPVT related to other pathologies such as Andersen-Tawil syndrome, and Long QT syndrome type 4 [5].

For the treatment of CPVT, beta-blockers are the most commonly used medication, despite their limited effectiveness. The combined use of beta-blockers, calcium antagonists, and flecainide has also been proposed, as well as sympathetic denervation and implantable cardioverter-defibrillator (ICD)[6]. Finally, high-impact activities and stressful situations should be avoided in all patients [6].

The following is a clinical case of a patient with CPVT, the report aims to draw the attention of the clinician to a cardiogenic syncope where CPVT should be kept under suspicion; also, to highlight the importance of molecular biology in the diagnostic approach of arrhythmias in pediatrics.

Case report

An 11-year-old female patient presented syncope while playing soccer, and three months later, repeated the episode while running. She had no personal pathological history of heart disease or sudden death in the family. During the interrogation, the patient stated that she had blurred vision and nausea in the presence of strong emotions. In the physical examination, weight and height were adequate for age, with no cardiovascular alterations. The parents denied changes in the family dynamics or the child's behavior. A tilt test was done, with a positive result for neurocardiogenic syncope of vasodepressor type, so the initial diagnosis was vasovagal syncope, managed with increased salt intake after the events.

At 13 years of age, the patient presented recurrent presyncope episodes triggered during exercise, 24 h Holter electrocardiogram was performed, which reported baseline sinus rhythm during most of the study, with occasional multifocal ventricular extrasystoles **(Figure 1).**

The recommendation was to avoid physical and emotionally stressful situations, and metoprolol 1.5 mg/kg/day was started simultaneously. Two months later, while swimming, she presented loss of consciousness accompanied by central cyanosis for 3 min. A transthoracic echocardiogram showed no abnormalities, with good biventricular function. He also underwent a modified stress test in which he reached 93% of maximum heart rate, observing ventricular extrasystoles since stage 2, initially monomorphic, suggestive of right ventricle outflow tract origin, then polymorphic and alternating in polarity, progressing in stage 3 to non-sustained polymorphic ventricular tachycardia event up to eight beats. Post stress, rapid recovery of sinus rhythm was achieved **(Figure 2 and 3).** Additionally, contrasted nuclear magnetic resonance was performed, which ruled out ventricular arrhythmogenic dysplasia. To determine genetic alterations that could explain the disease, the patient, parents, and siblings underwent a molecular panel for CPVT, a mutation in the RyR 2 gene (heterozygous c.14311G>A, p.V4771I) was detected in the patient.

With the diagnosis of CPVT and persistence of symptoms, the medical-surgical board decided to ablate with three-dimensional mapping with catheter array in the right ventricular outflow tract. Polymorphic ventricular tachycardia was easily induced with different extrasystoles that triggered it. The treatment partially modulated the initial discharge zones, but persists with the inducibility of foci, suggesting an origin in other areas of the right ventricle or left septal regions.

Given the poor response to the initial measures, an ICD was placed without complications, and propafenone 150 mg

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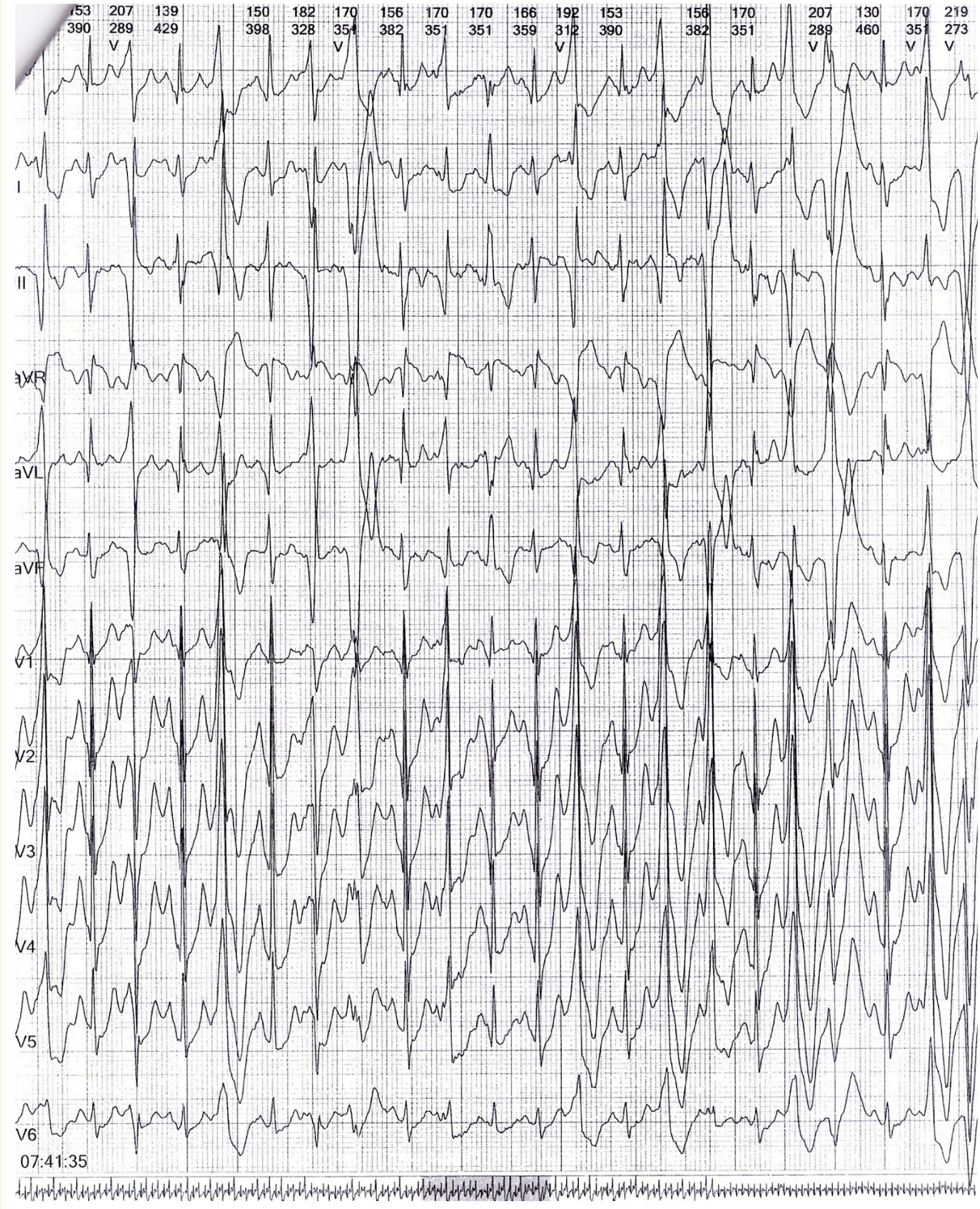

Figure 1. Trace from 24 h cardiac Holter: non-sustained ventricular extrasystoles

every 12 h was added to the therapy. Eight years later, the patient required three hospitalizations, and in the last one, amiodarone and carvedilol were prescribed, which considerably reduced the number of events. The patient has good adherence to treatment, to non-pharmacological measures, and continues in follow up by the electrophysiology service. However, the patient currently manifests a feeling of discomfort before the shocks and is anxious about the possibility that the device may not work.

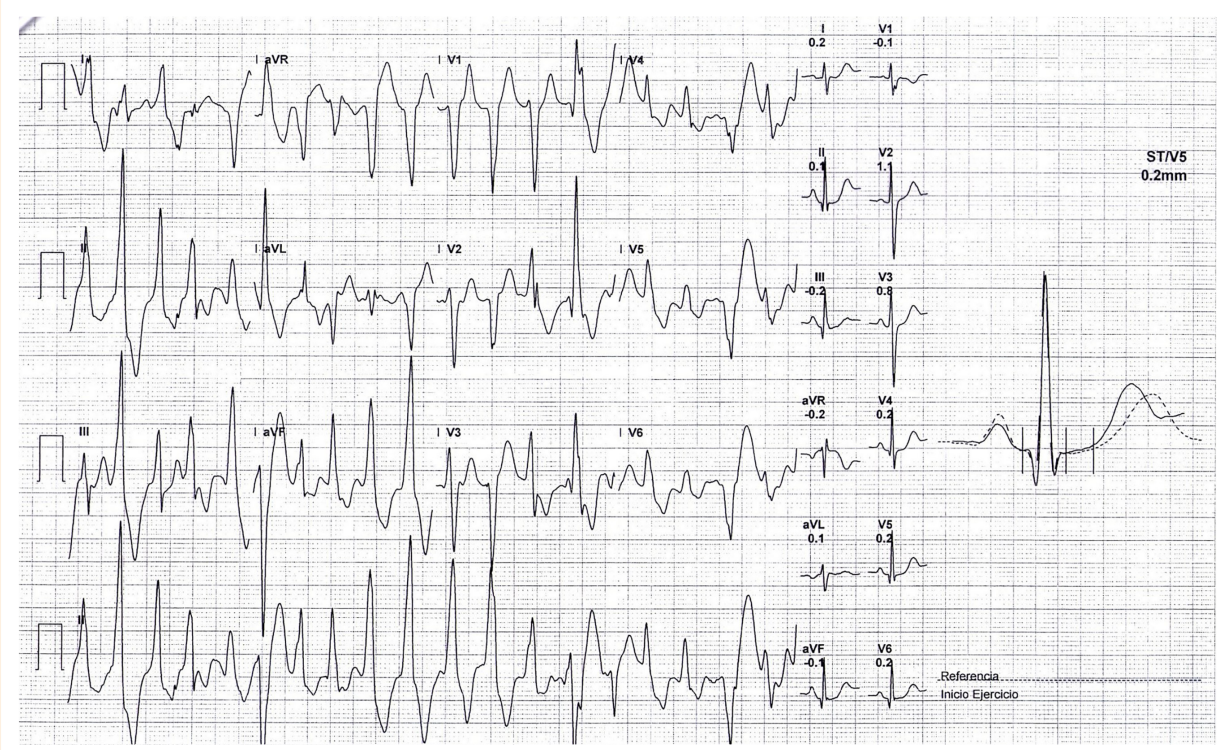

Figure 2. Modified stress test: polymorphic ventricular tachycardia after the second minute of exercise.

Discussion

Among the primary channelopathies, CPVT is one of the most lethal ones, has a high social impact due to the age group affected, and 40% of patients die within ten years after diagnosis [7]. The clinical manifestation, in our case, was exercise syncope; the guidelines recommend ECG as the first study in syncope, although in CPVT it is a dilemma due to the normality of the baseline rhythm [6]. Some case series report that up to 60% of patients are managed with other diagnoses related to vasovagal and neurological causes, causing a delay in the diagnosis of CPVT of up to 2 years [8,9], as happened in the present report, where the initial study was the tilt table test. Recently, the use of tilt test in children has presented controversies due to the variability of interpretation; in addition, a positive result does not rule out potentially deleterious causes and decision making based on it is not free of risks for the patient [10].

In this case, CPVT was suspected with the 24 h Holter results, and the diagnosis was established in the stress test with the progression of ventricular ectopic beats to polymorphic tachycardia, so genetic testing was performed [6]. The mutation described in this report was in the RyR2 gene, which is a large ion channel, in the cardiomyocyte its functional form is a homo-tetramer that regulates the release of calcium (Ca2+) from the sarcoplasmic reticulum to the cytosol during cardiac contraction [11]. Currently, there are about 150 registered RyR2 missense mutations, many of which are associated with the development of CPVT [12]; three hot spots have been identified where RyR mutations are generally clustered, which are located in the N-terminal (164-433), central (2,246-2,504) and C-terminal (3,778-4,959) domains [13].

The patient presented a missense mutation (c.14311G>A, p.v4771I) which is pathogenic and has been reported in association with CPVT [14] The mutation is in the C-terminal region that forms the pore of the channel. In this mutation there is a change of valine for isoleucine, although the change is of a non-polar amino acid for a non-polar one and involves small modifications in the physicochemical properties of hydrophobicity and mass, this valine residue is highly conserved among species and is located in one of the three hot spots for mutations with physiological potential, therefore, an important role of this mutation is associated in the gain of function of the RyR2 [13,15].

Several hypotheses explain why mutations in RyR2 allow CPVT, the most widely accepted is that the mutations

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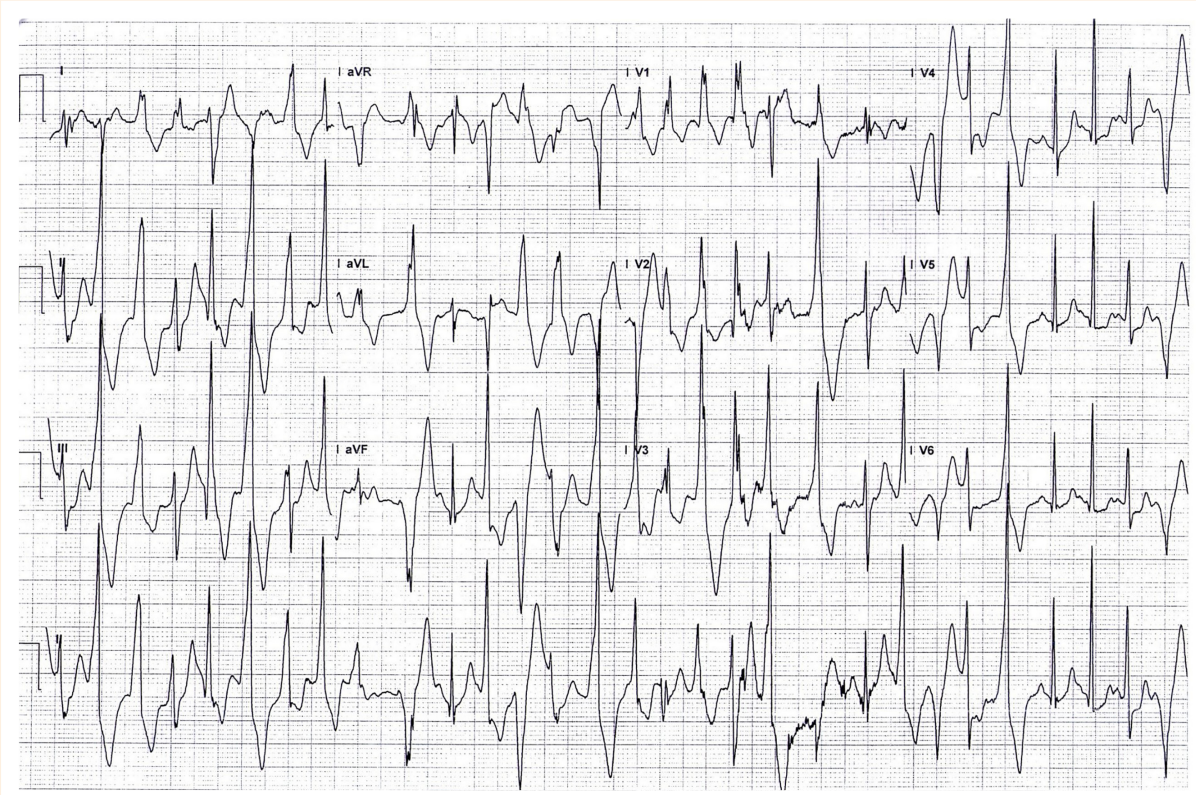

Figure 3. Polymorphic ventricular tachycardia in the recovery stage of the ergometry.

sensitize RyR2 channels to luminal calcium in the sarcoplasmic reticulum, allowing them to open at a lower intracellular calcium concentration, which has been termed store overload-induced calcium release (SOICR). According to this hypothesis, lowering the activation threshold allows calcium leakage during diastole, which induces arrhythmias [11]. Another more recent theory suggests that mutations alter the interdomain interaction, destabilizing channel closure and allowing leakage of Ca2+ contained in the sarcoplasmic reticulum [11,13].

Regarding the treatment of CPVT, the initial management of the patient was to reduce high impact activities and the administration of beta-blockers, the first line of management for this pathology [6], however, they are not sufficient to control the events, so catheter ablation should be needed. This procedure is an adjuvant therapy in refractory cases, although there are few reports of success [6,7], as evidenced in this patient. After therapeutic failure, ICD implantation was decided, which has been recommended in the guidelines [6,7]; however, it has been reported that 50% of children have inadequate discharges, generating pain, anxiety, and depression, increasing the risk of arrhythmias [16]. Propafenone, as well as flecainide, have been able to demonstrate inhibition of RyR2 activity with acceptable clinical results, although recent studies question the mechanism of action of flecainide on RyR2 [7], in some situations of recurrence it is necessary to use combinations of antiarrhythmics, as in this case [17]. Despite ICD`s side effects, the parents and the patient considered that the benefits of the treatment outweighed the risk of sudden death. Finally, recent research applying CRISPR/Cas9 gene-editing technology seems to be promising in this pathology [12].

Conclusion

It is important to consider CPVT in children with syncope induced by emotion or physical activity because of the severity of this condition; in countries such as Colombia, having molecular biology tools is essential for diagnosis and appropriate therapeutic intervention, as well as timely identification in relatives of CPVT patients, allowing pre-symptomatic diagnosis and genetic counseling.

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