https://doi.org/10.24207/jca.v32i2.006_IN

Sudden Death by Catecholaminergic Polymorphic Ventricular Tachycardia in Children

Morte Súbita por Taquicardia Ventricular Polimórfica Catecolaminérgica em Criança

Isabella João Milan[1,*], Fernando Mello Porto[2], Halim Cury Filho[2], Adão Bento de Lucena Neto[2], Jose Marco Nogueira Lima[2]

ORCID IDs

Milan IJ https://orcid.org/0000-0003-3497-3049
Porto FM https://orcid.org/0000-0003-1503-4273
Cury Filho H https://orcid.org/0000-0003-0102-4082
Lucena Neto AB https://orcid.org/0000-0001-6946-1217
Lima JMN https://orcid.org/0000-0002-9377-7649

ABSTRACT

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a severe cardiac arrhythmogenic hereditary illness, which affects children and young adults with a structurally healthy heart. Its prevalence is of one case in 10 thousand inhabitants. It is a potentially fatal illness, part of the differential diagnosis of syncope in children. The present study has the purpose of relating the case of a child that, during the investigation of convulsive syncope, presented sudden death aborted due to CPVT and to describe the diagnosis difficulties of the case, comparing with data from the literature.

KEYWORDS: Ventricular tachycardia; Cardiac sudden death; Tachycardia.

RESUMO

A taquicardia ventricular polimórfica catecolaminérgica (TVPC) é uma doença cardíaca arritmogênica grave, hereditária, que acomete crianças e adultos jovens com coração estruturalmente normal. Sua prevalência é de um caso em 10 mil habitantes. É uma doença potencialmente fatal, que faz parte dos diagnósticos diferenciais de síncope em criança. O presente trabalho tem como objetivo relatar o caso de uma criança que, durante investigação de síncope convulsiva, apresentou morte súbita abortada devido à TVPC e abordar as dificuldades diagnósticas do caso, comparando com dados da literatura.

PALAVRAS-CHAVE: Taquicardia ventricular; Morte súbita cardíaca; Taquicardia.

1.Hospital Municipal Dr. Mário Gatti – Clínica Médica – Campinas/SP – Brazil.
2.Grupo de Arritmia de Campinas – Campinas/SP – Brazil.
***Correspondence author:** isa_milan11@hotmail.com
Received: 18 Mar 2018 | **Accepted:** 5 Jul 2019
Section Editor: José Mario Baggio Junior

INTRODUCTION

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is a severe cardiac arrhythmogenic hereditary illness that affects children and young adults with a structurally healthy heart. It presents clinically as syncope, convulsive syncope or, in up to 30% of the cases, sudden death, in situations of physical distress or high emotions [1,2].

The possibility of CPVT must be taken into consideration when there is polymorphic adrenally-induced ventricular tachycardia, in the absence of any other cardiac structural or electric anormality[3,4]. Exams such as holter and, mainly, an ergometric test may consolidate the diagnosis hypothesis, since, when performing physical effort or going through situations of emotional distress the electrocardiogram may show polymorphic ventricular extra-systoles or even evoke ventricular tachycardia [5,6].

The diagnosis confirmation is done according to a genetic profile. The main gene involved is the dominant *RyR2*, a receptor of cardiac ryanodine, in approximately 60% of the cases[3,6-8]. However, other genes, such as autosomal recessive *CASQ2*, which codifies the cardiac calsequestrineque, among other less frequent, have already been confirmed as causers of the desease[4].

The prevalence of CPVT is of one case in every 10 thousand inhabitants and, although it is not so rare, it is an under-diagnosed illness due to a series of factors[4]. One of the causes of under-diagnosis is its presentation as syncope or convulsive syncope, which leads, many times, to a wrong primary diagnosis of vasovagal syncope or epilepsy[8]; another cause of under-diagnosis is due to the structurally healthy heart that, adding to the lack of knowledge of the disease, makes the cardiac pathology be discarded at the beginning of the investigation. Still, the genetic profile study for the confirmation of the diagnosis is not always accessible [3].

CPVT treatment is performed with behavioral measures, such as restraining intense physical activities and avoiding situations of strong emotions, in association to medicament therapy with beta-blockers as the first choice of pharmaceutical treatment, with the control of the disease in two thirds of the cases[2,4], and flecainide, antiarrhythmic from I-C class, not commercially available in Brazil, for the non-responders or intolerant to betablocking[9]. For refractory patients to the medicament therapy, there is still the option of left sympathetic denervation to diminish the CPVT and implantable cardiac defibrillators for the prevention of sudden death [5].

With that said, the purpose of this article was to contribute to the medical literature when presenting a case of sudden death aborted by CPVT in a child, with the diagnosis being difficult since exams of higher diagnostic accuracy were standard, aiming at a better understanding of the theme.

CASE REPORT

Patient GNA, male gender, Caucasian, brought by his mother for the first consultation four years ago, when presenting nine years of age, complaining of convulsive syncope in high emotional distress, physical exercises or pain. He had already been examined by a neuro pediatrician that, after the investigation, referred him to Cardiology. No other complains or comorbidity was mentioned, and no positive data on the family history was brought up.

For the initial investigation of the case, the following exams were performed: electrocardiogram, 24h holter, tilt-table-test, and maximum ergometric test. All the exams were within normal; however, the patient continued symptomatic. Then, the patient was submitted to the placement of an implantable looper, which showed an episode of sinusal pause during syncope, in a stressful situation due to traumatic pain.

The initial diagnosis was of vasovagal syncope, although the tilt-table-test was normal. It was chosen to maintain the implantable looper due to the exuberant clinical situation of the patient, which showed respiratory failure and cardiac arrest while performing physical activity. It was performed CPR, with the reversion of sudden death and the implantable looper identified polymorphic ventricular tachycardia.

Then, an invasive electrophysiological study was performed with endovenous isoprenaline and progressive ventricular stimulation; however, no tachyarrhythmia was induced. After this episode, as secondary prevention against sudden death, an implantable unicameral ventricular cardio defibrillator (ICD) was placed.

The genetic profile study was performed, which showed a mutation in the *RyR2* gene, confirming the diagnosis, starting the clinical treatment of beta-blocker, 40 mg of propranolol twice a day, not tolerating higher doses due to symptomatic hypotension.

Due to the intense anxiety of the patient, he performed many episodes of CPVT, followed by appropriate shocks of ICD, even with the use of beta-blocker. Reviewing

the literature, it was possible to notice that some cases of CPVT are refractory regarding the use of beta-blocker, indicating associating flecainide for the control of the disease. However, this antiarrhythmic medication is not commercialized in Brazil and, after judicial litigation, the patient started using 50 mg of flecainide twice a day and the propranolol was suspended, having clinical control of the appropriate therapies of ICD, remaining nowadays for 24 months without episodes of CPVT.

DISCUSSION

The CPVT is an arrhythmogenic hereditary potentially fatal illness, with mortality rate from 30% to 50% until 30 years of age in non-treated patients, highlighting the need of early diagnosis[1,3,5,10]. Due to the advanced age of its presentation, generally between seven and 12 years of age, and due to the patients having hearts without structural alterations, many receive the wrong diagnosis of orthostatic dysregulation or epilepsy, delaying, this way, the treatment for CPVT[5,11,12].

After the clinical suspicion of CPVT, non-invasive exams are performed by confirming the diagnosis hypothesis. The resting electrocardiogram is normal, just like the echocardiogram. In most cases, during the Holter test or, mainly, with effort during the ergometric test, polymorphic or bidirectional ventricular tachycardia is highlighted, when the patient goes through physical or emotional distress, ratifying the hypothesis diagnosis of CPVT When the effort test is stopped, the arrhythmias gradually disappear[5,10,11,13].

In the majority of the cases in which the non-invasive exams showed no alterations, the invasive electrophysiological exam may be performed in order to complement diagnosis, which highlights ventricular tachycardia with isoproterenol stimulation, sympathomimetic medication with mainly acts as beta-agonist, in 30 to 75% of the cases [11].

Diagnostic confirmation is performed through genetic study. Mutations in the gene that codifies the cardiac receptor of ryanodine, *RyR2*, are the most common alterations in CPVT, being present in approximately 60% of the cases. These mutations enhance the spontaneous diastolic liberation of calcium from the sarcoplasmic reticulum, mainly the presence of catecholamines, predisposing, therefore, ventricular tachycardia. In physiological situations, calcium should be removed from the intracellular medium in diastole by the exchange of calcium through the adenosine triphosphate (ATP) pump [2-4,6-8,13].

Besides the alteration in the dominant autossomic gene *RyR2*, the CPVT may also have a rarer genetic mutation, as in the case of *CASQ2* gene, which codifies the cardiac casequestrine and is of autossomic recessive inheritance. It is the second genetic variant of the disease, responsible for less than 5% of the cases. *CASQ2* gene is responsible for the calcium recaptation for the sarcoplasmic reticulum during diastole. Mutations in the gene diminish the calcium recaptation, mainly under adrenergic stress, which predetermines CPVT. Rare cases of CPVT may also be sporadic [1,4,6,9].

Initial treatment of CPVT consists of behavioral measurements, such as restraining intense physical activities and situations which may generate great emotional distress, and pharmaceutical therapy with the use of beta-blockers in the maximum tolerated dose, since, when blocking beta receptors, there is inhibition of the sympathetic stimulation, with good response to treatment in two thirds of the cases [1,3-6,9,12].

For one third of the refractory or intolerant patients to beta-blockers and that continue to present arrhythmic cardiac events, a beta-blocker by flecainide may be associated or substituted, which is an antiarrhythmic agent from class IC that, besides blocking sodium cardiac channels, directly inhibits *RyR2* gene, diminishing even more the percentage of patients that maintain symptoms and arrhythmic events[1-6].

For refractory patients to the maximum pharmaceutical treatment, there are still other therapeutic choices, such as ICD implant, indicated for all as secondary prevention against sudden death and also for those with very symptomatic CPVT, despite the pharmacotherapy. There is also the option of left cardiac sympathetic denervation for patients who habitually present syncope or polymorphic ventricular tachycardia[1,4,9,11].

The patient in this study presented classical clinical case, with starting convulsive syncopes at nine years of age, in situations of physical or emotional distress. However, the diagnosis was difficult, since all the non invasive exams presented usual, being the diagnosis of CPVT confirmed only after an aborted sudden death episode, situation in which the implantable looper demonstrated polymorphic ventricular tachycardia and the patient was

then submitted to genetic profile study that showed typical alteration of the disease, the mutation in the *RyR2* gene.

The patient's treatment was also tricky since due to intense symptomatology, the patient suffered bullying at school, worsening the emotional distress and, therefore, the convulsive syncopes. Also, he presented intolerance to first choice pharmaceutical therapy, the beta-blocker, for presenting symptomatic hypotension. Then, the following adversity was to obtain the flecainide, since the drug is not commercially available in Brazil, demanding judicial litigation for its liberation.

However, after the use of flecainide, the patient showed a completely positive response to the treatment, remaining asymptomatic for 24 months, without the need for additional therapies. He still uses ICD as secondary prevention against sudden death but does not do any additional therapy since the introduction of flecainide.

AUTHORS' CONTRIBUTION

Conceptualization, Milan I.J., and Porto F.M.; Methodology, Milan I.J.; Investigation, Filho H.C, Neto A.B.L, Lima J.M.N.; Writing– First version, Milan I.J.; Writing – Revision & Editing, Milan I.J. and Porto F.M.; Supervision, Porto F.M.

REFERENCES

1. Atik SU, Alp FE, Dedeoğlu R, Koka A, Öztunç F, Eroğlu AG. A rare cause of sudden cardiac arrest: catecholaminergic polymorphic ventricular tachycardia. Turk Pediatri Ars. 2018;53(2):124-8. https://doi.org/10.5152/TurkPediatriArs.2017.3899.

2. Pérez FW, Afonso JSH, Marco MVG, Dorta EC, Acosta LA, Larrea OC, et al. Flecainide reduces ventricular arrhythmias in patients with genotype RyR2-positive catecholaminergic polymorphic ventricular tachycardia. Rev Esp Cardiol. 2018;71(3):185-91. https://doi.org/10.1016/j.rec.2017.04.032

3. Duan H, Lu Y, Qiao L, Hua Y, Li Y, Zhou K, et al. A delayed diagnosis of catecholaminergic polymorphic ventricular tachycardia with a mutant of RYR2 at c.7580T>G for 6 years in a 9-year-old child. Medicine. 2018;97(16):1-5. https://doi.org/10.1097/MD.0000000000010368

4. Velcea AE, Siliste C, Vinereanu D. Catecholaminergic polymorphic ventricular tachycardia – Looking to the future. Maedica (Buchar). 2017;12(4):306-10.

5. Napolitano C, Priori SG, Bloise R. Catecholaminergic polymorphic ventricular tachycardia. Gene Reviews. 2004; 633-39. https://doi.org/10.1016/B0-7216-0323-8/50071-3

6. Pölönen RP, Penttinen K, Swan H, Aalto-Setälä K. Antiarrhythmic effects of carvedilol and flecainide in cardiomyocytes derived from catecholaminergic polymorphic ventricular tachycardia patients. Stem Cells Int. 2018; https://doi.org/10.1155/2018/9109503

7. Lieve KVV, Verhagen JMA, Wei J, Bos JM, Werd C, Noguer FR, et al. Linking the heart and the brain: neurodevelopmental disorders in patients with catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm. 2018;32(18):30826-9. https://doi.org/10.1016/j.hrthm.2018.08.025

8. Pan X, Phillippen L, Lahiri SK, Lee C, Park SH, Word TA, et al. In vivo Ryr2 editing corrects catecholaminergic polymorphic ventricular tachycardia. Circ Res. 2018;123(8):953-63. https://doi.org/10.1161/CIRCRESAHA.118.313369

9. Seidlmayer LK, Riediger F, Pagonas N, Nordbeck P, Ritter O, Sasko B. Description of a novel RyR2 mutation in a juvenile patient with symptomatic catecholaminergic polymorphic ventricular tachycardia in sleep and during exercise: a case report. J Med Case Rep. 2018;12(1). https://doi.org/10.1186/s13256-018-1825-6

10. Ylänen K, Poutanen T, Hiippala A, Swan H, Korppi M. Catecholaminergic polymorphic ventricular tachycardia. Eur J Pediatr. 2010;169(5):535-42. https://doi.org/10.1007/s00431-010-1154-2

11. Velasco A. Taquicardia ventricular polimórfica catecolaminérgica Rev Colom Cardiol. 2009;16(2):71-5.

12. Fujita S, Nishida K, Nakagawa R, Futatani T, Igarashi N, Usuda K, et al. Catecholaminergic polymorphic ventricular tachycardia managed as orthostatic dysregulation and epilepsy in 11- and 15-year-old sisters. Pediatr Int. 2018;60(11):998-1001. https://doi.org/10.1111/ped.13688

13. Domingo, AM. Genética de la taquicardia ventricular polimorfa catecolaminérgica; conceptos básicos. Arch Cardiol Méx. 2008;79(2):13-7.

14. Leite LR, Pereira KRP, Alessi SRB, Paola AAV. Taquicardia ventricular polimórfica catecolaminérgica. um importante diagnóstico em crianças com síncope e coração estruturalmente normal. Arq Bras Cardiol. 2001;76(1):63-8.

15. Oliveira ARF, Santiago GSL, Júnior EFX, Moser LRDN, Mourato FA, Mattos SS. Taquicardia ventricular polimórfica catecolaminérgica com morte súbita abortada. Rev Bras Cardiol. 2014;27(5):382-4.