Case Study

International Journal of Cardiology and Cardiovascular Disorder

A Novel Ryr2 Mutation in an Adult Patient with Cardiac Arrest Caused by Ventricular Arrhythmia Suspected to be Catecholaminergic Polymorphic Ventricular Tachycardia: A Case Report

Phan Thai Hao M. D, PhD[1,2*], Phan Tuan Anh Kiet M.D.[2]

[1]*Pham Ngoc Thach University of Medicine, HCM city, Vietnam.*

[2]*HCMC Hospital for Rehabilitation-Professional Diseases.*

***Correspondence author**
Phan Thai Hao, M.D, Ph.D.
HCMC Hospital for Rehabilitation-Professional Diseases
Pham Ngoc Thach University of Medicine,
HCM city, Vietnam.

Submitted : 16 Oct 2023 ; Published : 31 Oct 2023

Citation: Phan T. Hao *et.al* (2023). A Novel Ryr2 Mutation in an Adult Patient with Cardiac Arrest Caused by Ventricular Arrhythmia Suspected to be Catecholaminergic Polymorphic Ventricular Tachycardia: A Case Report. I J cardio & card diso 4(3): 1-3.

Abstract

Inherited arrhythmia syndromes remain an important and increasingly recognized cause of ventricular tachycardia (VT) and sudden cardiac death. Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare but potentially lethal, heritable cardiac arrhythmia that occurs in response to physical or emotional stress, it often manifests as exercise-induced ventricular arrhythmias, syncope, or sudden death. If untreated, catecholaminergic polymorphic ventricular tachycardia is a highly lethal condition: About 80% of affected individuals experience recurrent syncope, and 30% experience cardiac arrest. CPVT is caused by mutations in genes encoding proteins involved in calcium handling in cardiomyocytes, such as the cardiac ryanodine receptor (RyR2). RyR2 mutations impair the regulation of calcium release from the sarcoplasmic reticulum, leading to delayed afterdepolarizations and triggered arrhythmias. Here, we report a case of CPVT in a patient with RyR2 gene mutation, causing sudden cardiac arrest.

Keywords: Novel gene mutation; Ryanodine receptor type 2 (RyR2); Cardiac arrest; Catecholaminergic polymorphic ventricular tachycardia.

Background

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited disorder characterized by electrical instability in the cardiac myocytes resulting from activation of the adrenergic system (Behere & Weindling, 2016; Pérez-Riera et al., 2018). CPVT has been noted to have an autosomal inheritance, with certain gene mutations being dominant, such as CALM1 and RYR2 (ryanodine receptor-2), while others have a recessive pattern, namely CASQ2 and TRDN (Napolitano et al., 2022). CPVT is associated with syncope due to ventricular tachycardias, either fast polymorphic ventricular tachycardia (VT) or bidirectional VT (Pérez-Riera et al., 2018). The onset of symptoms for CPVT is predominantly seen early in life, ages seven to twelve; however, there are also reports of patients presenting as late as in the fourth decade of life (Behere & Weindling, 2016). In at least 30% of patients, a sudden cardiac arrest has been documented, while 80% of patients will experience at least one or more syncopal episodes (Napolitano et al., 2022). This report presents a case of RYR2 gene mutation causing fast polymorphic VT resulting in sudden cardiac arrest at 28 years of age.

Case Presentation

A 28-year-old male patient who suffered an out-of-hospital cardiac arrest was successfully resuscitated before being transferred to our hospital. Field evaluation revealed an initial rhythm of ventricular fibrillation. The patient had a history of palpitations and syncope since childhood, but was never diagnosed with CPVT. His family history was unremarkable. He collapsed at his house and was resuscitated with an automated external defibrillator in a local hospital, he then returned to spontaneous circulation but suffered sustained post-cardiac arrest brain injury. His vitals at admitting included a temperature of 37 C, heart rate of 100 bpm, blood pressure of 100/60 mmHg, respiratory rate of 18/min, and oxygen saturation of 97% in room air. Initial workup, including but not limited to complete blood count, comprehensive metabolic panel, and other electrolytes, troponins, brain natriuretic peptide (BNP), were within normal limits. Initial electrocardiogram (ECG) showed sinus tachycardia with a QTc of 456 ms (Figure 1).A transthoracic echocardiogram (TTE) was performed which revealed no structural abnormality. The patient underwent genetic testing during his time in the hospital. The genetic test revealed a novel heterozygous missense mutation in RyR2 (c.6251T>C, p.Met2084Thr). On the chromosome 1, at the nucleotide number 6251, Thymine was replaced by Cytosine,

causing the protein 2048 Methionine to be replaced by Threonine (Table 1). The patient was treated with bisoprolol 5 mg daily. Since after being hospitalized, the patient did not have any newly-onset recorded episode of ventricular arrhythmia.

RESULT							
Gene	**Inheritance**	**Zygosity**	**Position**	**Alteration**	**Consequence**	**Phenotype**	**Variant Classification in Clinvar**
RYR2	Autosomal dominant	Heterozygous	chr1: 237627891	NM_001035.3: c.6251T>C (NP_001026.2: p.Met2084Thr)	missense variant	1. Ventricular arrhythmias due to cardiac ryanodine receptor calcium release deficiency syndrome 2. Ventricular tachycardia, catecholaminergic polymorphic, 1	Non-Clinvar variant

Table 1: Gene result test

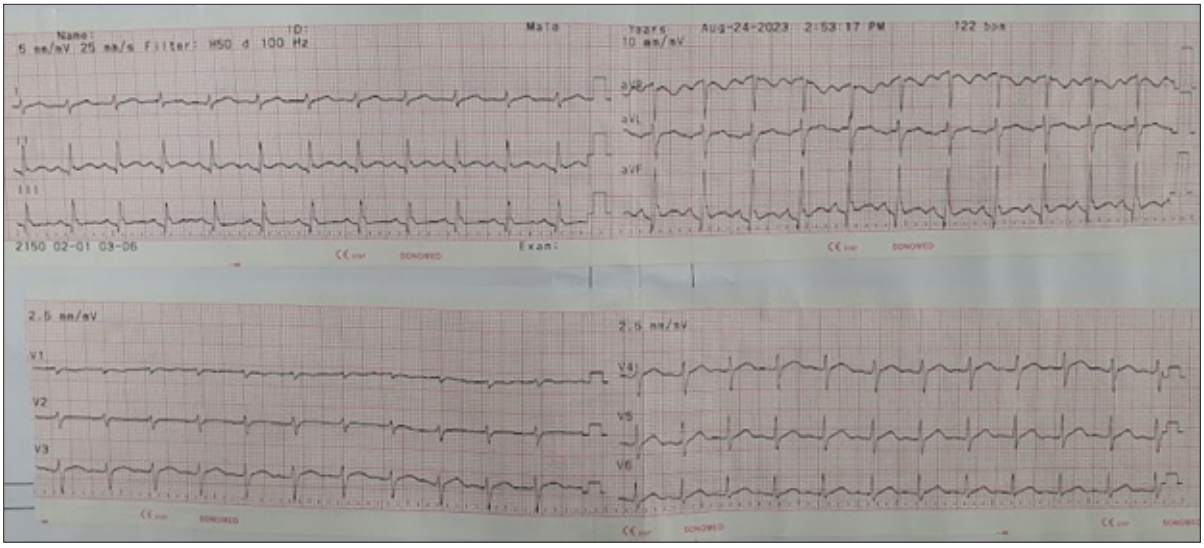

Figure 1: Electrocardiography at admission

Discussion

We describe a case of a patient presenting with cardiac arrest caused by ventricular arrhythmia suspected to be catecholaminergic polymorphic ventricular tachycardia (CPVT) secondary to a novel RyR2 mutation. CPVT is a rare inherited disorder that affects one out of every 10,000 people. It is characterized by an excessive sympathetic tone (emotional or physical) leading to lethal ventricular arrhythmias (Behere & Weindling, 2016). Out of all documented CPVT cases, the RYR2 mutations encompass 60% of cases (Marquez et al., 2019). The RYR2 gene encodes the calcium (Ca2+) release channel receptor located in the sarcoplasmic reticulum of cardiomyocytes which has an important role in cardiac excitation-contraction coupling (Lehnart et al., 2008; Postma et al., 2005). Mutations in the RYR2 gene result in prolonged calcium channel opening with subsequent calcium leak during diastole leading to an increased risk of ventricular arrhythmias and death (Marquez et al., 2019). Major symptomatology includes syncope, sudden cardiac arrest and death, while minor symptoms include dizziness, palpitations, and chest pain. Common arrhythmias include polymorphic ventricular tachycardia (PMVT) or bidirectional VT, both of which can propagate into ventricular fibrillation(Behere & Weindling, 2016). Diagnosing CPVT with standard ECG can be challenging as most of these patients usually do not have any baseline abnormalities at rest (Behere & Weindling, 2016). Exercise stress testing can be an important diagnostic test for CPVT as ventricular arrhythmias are manifested with an increased heart rate (110-130 beats per minute). The arrhythmias can gradually resolve as the heart rate slows down. An important consideration is that negative stress testing does not completely rule out CPVT. Extended cardiac monitoring devices can be useful in instances where stress testing is inconclusive(Behere & Weindling, 2016).

Diagnostic criteria proposed by Prior et al. (2013):

1. The presence of a normal structural heart and normal EKG and unexplained stress-induced bidirectional VT or PMVT in individuals younger than 40 years old;
2. Finding a pathogenic mutation;
3. and the presence of unexplained stress-induced bidirectional VT or PMVT in a first-degree family member, who has no structural heart abnormalities;
4. Presence of a normal structural heart and normal EKG and unexplained stress-induced bidirectional VT or PMVT in individuals older than 40 years old.

Patients diagnosed with CPVT are highly recommended to avoid physical stress, such as participating in high-intensity exercise and any form of activities involving high adrenergic output. It is also imperative that patients are counseled on

strict medication adherence(Pérez-Riera et al., 2018, Lieve et al., 2018). Pharmacologically, beta-blockers have been the mainstay of the treatment of CPVT. Of these medications, the long-acting beta-blocker nadolol is preferred (Ackerman et al., 2017). Carvedilol has also been shown to be effective by inhibiting RYR2 activity(Pérez-Riera et al., 2018). Almost 30-40% of patients experience symptoms despite beta-blockers, requiring implantable cardioverter-defibrillator (ICD) therapy (Lieve et al., 2018). Calcium channel blockers like verapamil have also been used to treat ventricular arrhythmias in CPVT, especially in patients with CASQ2 gene mutation (Behere & Weindling, 2016; Pérez-Riera et al., 2018; Lieve et al., 2018). Also, ICD can be considered in patients if symptoms persist despite optimal medical therapy (Behere & Weindling, 2016; Pérez-Riera et al., 2018). Genetic counseling is essential for first-degree relatives, as they should be evaluated for mutations to decrease the risk of future unwarranted and preventable adverse events (Pflaumer & Davis, 2012).

Conclusions

CPVT is a complex disease that carries a risk of sudden cardiac death in various age groups, with those at risk, including the younger population. We present a case of catecholaminergic polymorphic ventricular tachycardia associated with a novel single point mutation in the RyR2 gene. This case illustrates the importance of early recognition and management of CPVT, as well as the potential role of genetic testing in identifying the mutation causing CPVT. Beta-blockers, calcium channel blockers and, flecainide are the main pharmacological agents employed, with sympathetic denervation and ICD being used in refractory cases.

References

1. Behere, S. P., & Weindling, S. N. (2016). Catecholaminergic polymorphic ventricular tachycardia: An exciting new era. *Annals of Pediatric Cardiology, 9*(2), 137-46. DOI: https://doi.org/10.4103/0974-2069.180645
2. Pérez-Riera, A. R., Barbosa-Barros, R., de Rezende Barbosa, M. P. C., Daminello-Raimundo, R., de Lucca, Jr A. A., & de Abreu, L. C. (2018). Catecholaminergic polymorphic ventricular tachycardia, an update. *Annals of Noninvasive Electrocardiology, 23*(4), e12512. DOI: https://doi.org/10.1111/anec.12512
3. Napolitano, C., Mazzanti, A., Bloise, R., Priori, S. G. (2022). Gene Reviews. In M. P. Adam, G. M. Mirzaa, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. W. Gripp, & A. Amemiya (Eds.), Catecholaminergic Polymorphic Ventricular Tachycardia. Seattle (WA). Retrieved from https://pubmed.ncbi.nlm.nih.gov/20301466/
4. Marquez, M. F., Totomoch-Serra, A., Rueda, A., Avelino-Cruz, J. E., & Gallegos-Cortez, A. (2019). Basic and Clinical Insights in Catecholaminergic (Familial) Polymorphic Ventricular Tachycardia. *Rev Invest Clin, 71*(4), 226-36. DOI: https://doi.org/10.24875/ric.19002939
5. Lehnart, S. E., Mongillo, M., Bellinger, A., Lindegger, N., Chen, B-X., Hsueh, W., Reiken S, Wronska, A., Drew, L. J., Ward, C. W., Lederer, W. J., Kass, R. S., Morley, G., Marks, A. R. (2008). Leaky Ca2+ release channel/ryanodine receptor 2 causes seizures and sudden cardiac death in mice. *The Journal of Clinical Investigation, 118*(6), 2230-45. DOI: https://doi.org/10.1172/jci35346
6. Postma, A. V., Denjoy, I., Kamblock, J., Alders, M., Lupoglazoff, J-M., Vaksmann, G., Dubosq-Bidot, L., Sebillon, P., Mannens, M. M., Guicheney, P., & Wilde, A. A. (2005). Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients. *Journal of Medical Genetics, 42*(11), 863-70. DOI: https://doi.org/10.1136/jmg.2004.028993
7. Priori, S. G., Wilde, A. A., Horie, M., Cho, Y., Behr, E. R., Berul, C., Blom, N., Brugada, J., Chiang, C. E., Huikuri, H., Kannankeril, P., Krahn, A., Leenhardt, A., Moss, A., Schwartz, P. J., Shimizu, W., Tomaselli, G., & Tracy, C. (2013). Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. *Heart Rhythm, 10*(12), e85-108. DOI: https://doi.org/10.1016/j.hrthm.2013.07.021
8. Lieve, K. V., van der Werf, C., & Wilde, A. A. (2018). Catecholaminergic Polymorphic Ventricular Tachycardia. *Circulation Journal, 80*(6), 1285-91. DOI: https://doi.org/10.1253/circj.cj-16-0326
9. Ackerman, M. J., Priori, S. G., Dubin, A. M., Kowey, P., Linker, N. J., Slotwiner, D., Triedman, J., Van Hare, G. F., & Gold, M. R. (2017). Beta-blocker therapy for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia: Are all beta-blockers equivalent? *Heart Rhythm, 14*(1), e41-e4. DOI: https://doi.org/10.1016/j.hrthm.2016.09.012
10. Pflaumer, A., & Davis, A. M. (2012). Guidelines for the diagnosis and management of Catecholaminergic Polymorphic Ventricular Tachycardia. *Heart Lung Circ, 21*(2), 96-100. DOI: https://doi.org/10.1016/j.hlc.2011.10.008