Scared to death—A novel mutation in catecholaminergic polymorphic ventricular tachycardia

Nikhil Jain, MD,* Jaime C. Holbert, DO, MS,* William Black, MD,* Reem Hussein, MD,* Gayathri Baljepally, MD, FACC,† Jeffrey Hirsh, MD, FACC, FHRS†

*From the *University of Tennessee Medical Center, Graduate School of Medicine, Knoxville, Tennessee, and †Cardiology, University of Tennessee Medical Center, Knoxville, Tennessee.*

Introduction

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare familial cardiac arrhythmia that results in bidirectional and polymorphic ventricular dysrhythmias often leading to sudden cardiac death.[1–3] These events are frequently triggered by exercise or emotional distress. CPVT typically occurs in patients with structurally normal hearts and often presents during childhood, with a mean age of presentation of 10 years.[1–4] CPVT can be inherited in an autosomal dominant (RYR2, KCNJ2, CALM1) or autosomal recessive (CASQ2, TRDN) pattern.[5,6] The autosomal dominant form is responsible for 60% of cases and is most often due to a mutation in the *RYR2* gene, which encodes for the cardiac ryanodine receptor 2.[6] The *CASQ2* gene, the most common autosomal recessive form, encodes for the protein calsequestrin-2 and is responsible for 1%–2% of cases of CPVT.[2,3,5–7] We report a novel genetic mutation in the *CASQ2* gene identified in a young female subject diagnosed with CPVT.

Case report

Our patient is a woman in her 30s, of Middle Eastern descent, with a history of hypercholesterolemia and purported epilepsy, who presented to the cardiology clinic for evaluation of recurrent syncope. She was diagnosed with epilepsy at a young age in her native country and was started on carbamazepine. She had been on carbamazepine for several years but continued to have syncopal episodes that were attributed to seizures. She had recently migrated to the United States and had more frequent syncopal spells. These episodes typically occurred in a public setting when she was overcome with fear and panic. Her husband reported observing full body rigidity and teeth clenching. The patient described feeling palpitations but denied any chest pain, dyspnea, or dizziness prior to syncope. The patient also reported a family history of sudden death; her brother died suddenly at age 20 but the

KEY TEACHING POINTS

- Inherited arrhythmia syndromes are often difficult to diagnosis and require a high level of clinical suspicion. Many patients go undiagnosed for years, as their symptoms are often nonspecific and arrhythmias may be infrequent and thus difficult to capture on telemetry. Electrocardiogram stress test is the current gold standard of diagnosis.
- The most common gene involved in catecholaminergic polymorphic ventricular tachycardia (CPVT) is the *RYR2* gene, which encodes for the cardiac ryanodine receptor 2. The *CASQ2* gene encodes for the protein calsequestrin-2 and is responsible for 1%–2% of cases of CPVT.
- The decision to implant an implantable cardioverter-defibrillator in patients with CPVT is challenging, as there are no randomized controlled prospective trials to evaluate the effectiveness and appropriateness in this patient population. Consideration for risk of inappropriate device therapies, implantation complications, device failure, and risk of sudden cardiac death needs to be a component of the shared decision-making process.

KEYWORDS Catecholaminergic polymorphic ventricular tachycardia; *CASQ2* mutation (c.101T>G; p.Val34Gly); Syncope; Sudden cardiac death; Genetic polymorphisms

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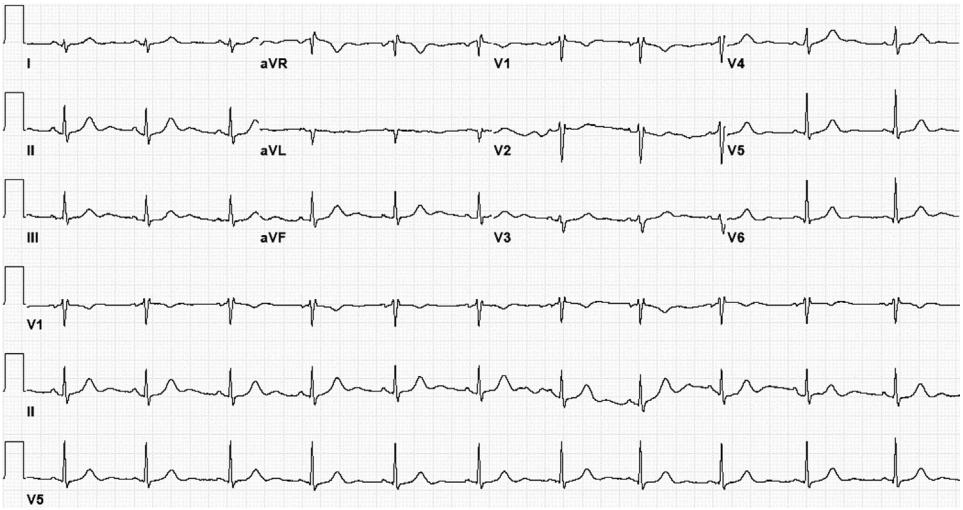

Figure 1 Baseline electrocardiogram showing sinus rhythm with heart rate of 67 beats per minute, QTc duration of 426 ms, and no significant abnormalities.

details surrounding his death were unclear. She has no other siblings and her parents have no history of syncope. She and her husband have 2 young sons, neither of whom have experienced syncope.

Initial electrocardiogram (ECG) showed normal sinus rhythm with T-wave inversion in V_1 and QTc of 426 ms (Figure 1). The patient's presentation and family history raised the possibility of an inherited channelopathy or other cardiac rhythm disorder. Long QT syndrome (LQTS) is the most common ion channelopathy, but her ECG was not suggestive of this potential diagnosis.[3] In order to further clarify her syncope, the patient was asked to wear an ambulatory ECG monitor for 24 hours. The ECG monitor showed sinus tachycardia with the development of bidirectional couplets, which then deteriorated into polymorphic ventricular tachycardia (Figure 2) before spontaneous return to normal sinus rhythm. An echocardiogram was performed which revealed no structural abnormality. Cardiac magnetic resonance imaging showed no structural abnormalities or late gadolinium enhancement. Based on history and ventricular arrhythmia on ambulatory monitor, she was diagnosed with CPVT.

The patient was optimized on medical therapy in addition to device therapy.[8,9] She was referred for genetic evaluation and a comprehensive arrhythmia and cardiomyopathy panel were obtained. The arrhythmia panel was notable for a homozygous missense mutation of *CASQ2*, c.101T>G, with valine replaced by glycine at codon 34 (p.Val34Gly). She was also heterozygous for a missense mutation in *ANK2*, which has been associated with autosomal dominant LQTS type 4.[3]

Discussion

We describe a case of a patient presenting with recurrent syncopal episodes and polymorphic ventricular tachycardia on ambulatory heart monitor who was subsequently diagnosed with CPVT secondary to a novel mutation of *CASQ2*—a homozygous missense mutation of *CASQ2*, c.101T>G with valine replaced by glycine at codon 34 (p.Val34Gly). This mutation results in a nonconservative amino acid change in the encoded protein sequence, but no data have been published to date that describe its impact on protein function.[10] The *CASQ2* gene codes for cardiac calsequestrin, the major calcium binding protein in the sarcoplasmic reticulum.[5] Mutations in *CASQ2* cause inappropriate and spontaneous calcium release from the sarcoplasmic reticulum that is enhanced by beta-adrenergic stimulation, leading to triggered arrhythmias. Though a myriad of mutations of *CASQ2* have been described in the literature, the phenotypic presentation of CPVT remains the same.[3,5,7]

The patient's genetic testing did report heterozygosity for a missense mutation in *ANK2*, which has been associated with autosomal dominant long QT syndrome type 4. Diagnostic criteria for LQTS have been well established and are based on ECG findings, clinical history, and family history.[3] Her resting ECG was not consistent with the LQTS diagnostic criteria, so it was felt that this diagnosis was less likely the source of her syncope.

Fortunately, an ion channelopathy was considered as a potential diagnosis and an outpatient monitor was ordered which recorded her spontaneous, potentially fatal, ventricular arrhythmia. She was initiated on appropriate medical therapy with use of implantable cardioverter-defibrillator as a safety adjunct given her high-risk findings on ambulatory monitoring and her family history of sudden death. Her medical therapy was further optimized with reduction in ventricular ectopy. Genetic analysis not only confirmed the diagnosis of *CASQ2*-related CPVT, but also reported a novel mutation.[10]

The patient's 2 young children were referred for genetic testing.

Conclusion

CPVT is typically an autosomal dominant condition due to mutations in *RYR2*. Mutations in *CASQ2* are much less

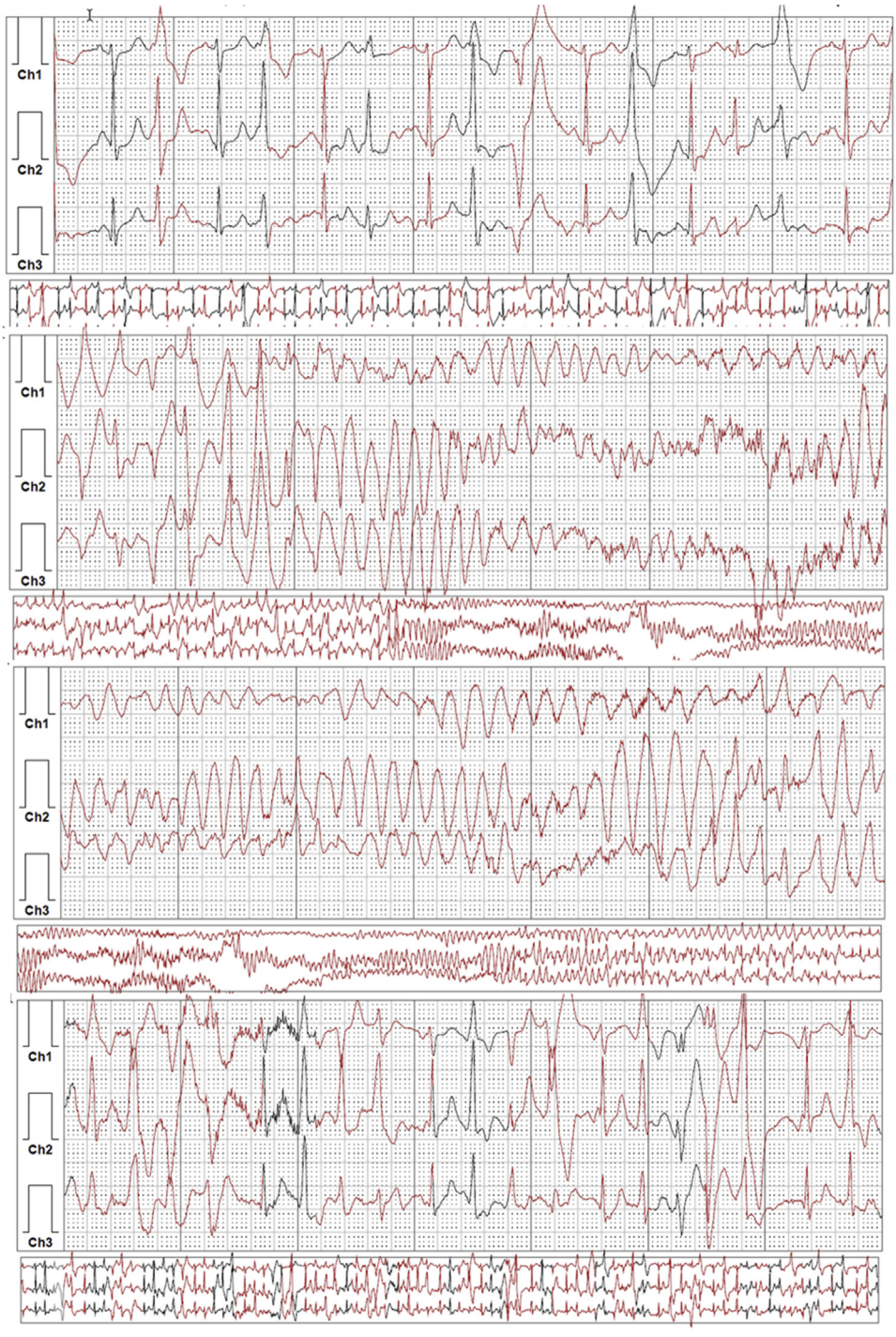

Figure 2 Ambulatory electrocardiogram monitoring demonstrating bidirectional couplets followed by polymorphic ventricular tachycardia, with subsequent spontaneous conversion back to sinus rhythm.

common, accounting for 1%–2% of cases, but have been well described in the literature. We report a novel *CASQ2* missense mutation associated with CPVT—a homozygous missense mutation of *CASQ2*, c.101T>G with valine replaced by glycine at codon 34 (p.Val34Gly). To our knowledge, this is the first reported case of CPVT associated with this specific mutation.

References

1. Napolitano C, Priori SG. Diagnosis and treatment of catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm 2007;4:675–678.
2. Napolitano C, Priori SG, Bloise R. Catecholaminergic polymorphic ventricular tachycardia. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews® [Internet]. Seattle WA: University of Washington, Seattle; 2004. 1993-2020.
3. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in

May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm 2013;10:1932–1963.
4. Cerrone M, Napolitano C, Priori SG. Catecholaminergic polymorphic ventricular tachycardia: a paradigm to understand mechanisms of arrhythmias associated to impaired Ca(2+) regulation. Heart Rhythm 2009; 6:1652–1659.
5. Roston TM, Yuchi Z, Kannankeril PJ, et al. The clinical and genetic spectrum of catecholaminergic polymorphic ventricular tachycardia: findings from an international multicentre registry. Europace 2018;20:541–547.
6. Wanguemert F, Bosch Calero C, Perez C, et al. Clinical and molecular characterization of a cardiac ryanodine receptor founder mutation causing catecholaminergic polymorphic ventricular tachycardia. Heart Rhythm 2015;12:1636–1643.
7. Roston TM, Haji-Ghassemi O, LaPage MJ, et al. Catecholaminergic polymorphic ventricular tachycardia patients with multiple genetic variants in the PACES CPVT Registry. PLoS One 2018;13. e0205925.
8. Hayashi M, Denjoy I, Extramiana F, et al. Incidence and risk factors of arrhythmic events in catecholaminergic polymorphic ventricular tachycardia. Circulation 2009;119:2426–2434.
9. Roston TM, Jones K, Hawkins NM, et al. Implantable cardioverter-defibrillator use in catecholaminergic polymorphic ventricular tachycardia: a systematic review. Heart Rhythm 2018;15:1791–1799.
10. National Center for Biotechnology Information. ClinVar [VCV000633142.2], https://www.ncbi.nlm.nih.gov/clinvar/variation/VCV000633142.2. Accessed October 18, 2019.