Hypertrophic cardiomyopathy and long QT syndrome in cardiac-only Timothy syndrome

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Introduction

While structural heart disease and cardiac channelopathies are often considered to have unique molecular mechanisms, genetic variations in the *CACNA1C* gene have been associated with hypertrophic cardiomyopathy (HCM) or long QT syndrome (LQTS).[1] *CACNA1C* encodes the L-type voltage-gated calcium channel that is responsible for many cardiac functions, including the plateau phase of the cardiac action potential and cellular excitability.[2] Gain-of-function mutations can result in Timothy syndrome (TS), with neurodevelopmental delay, syndactyly, and prolonged QT interval with malignant ventricular arrhythmia.[3] Here, we discuss a variant of this syndrome in a case of cardiac-only Timothy syndrome (COTS) with HCM and LQTS.

Case report

A 34-year-old man was referred for genetic evaluation of HCM, prolonged QT interval, and syncope. Over the preceding 4 years, he had experienced 3 episodes of syncope that were suspected to be orthostatic in nature following dehydration or standing quickly. There was no history of developmental delay. Review of prior electrocardiogram (ECG) demonstrated normal sinus rhythm with a corrected QT interval of 466 ms, left ventricular hypertrophy (LVH), and premature atrial complexes. The physical examination revealed a normal rate, regular rhythm, and a grade III/VI systolic murmur that was louder with Valsalva. There was no physical evidence of heart failure, syndactyly, or premature baldness. He was very active at baseline, exercising multiple times per week in the form of endurance aerobic and resistance training. Aside from the few instances of orthostatic lightheadedness and syncope, he was asymptomatic.

KEY TEACHING POINTS

- Timothy syndrome exhibits a spectrum of clinical presentations and severity.
- Cardiac-only Timothy syndrome (COTS) is limited to the heart.
- Prolonged QTc intervals may accompany cardiomyopathy nonspecifically; however, when it coincides with hypertrophic cardiomyopathy, COTS should be considered and *CACNA1C* should be included in genetic screening panels.
- In cases where a *CACNA1C* mutation is observed, careful evaluation for subclinical involvement of noncardiac tissues is warranted.

His vital signs were notable for resting bradycardia. He was prescribed metoprolol succinate 25 mg once daily; however, this caused grogginess and erectile dysfunction. The patient had a remote history of mitral valve regurgitation. He has a family history of HCM in his father and HCM with sudden cardiac death in a maternal uncle (Figure 1). The initial diagnosis for the proband was HCM with nonspecific QT prolongation accompanying the cardiomyopathy. Consideration was given to possible underlying primary channelopathies, including hereditary LQTS.

Initial ECG showed sinus bradycardia, LVH, and variably prolonged QTc (562–590 ms) (Figure 2A). Echocardiogram demonstrated LVH with asymmetric septal hypertrophy (Figure 2B). Cardiac magnetic resonance imaging showed a mildly depressed left ventricle ejection fraction of 47% (Figure 2C). There was severe basal septal and anterior wall hypertrophy with a maximal wall thickness of 31 mm. The mitral valve had systolic anterior motion with regurgitation. There was flow acceleration across the left ventricular outflow tract. Patchy foci of late gadolinium enhancement within the basal anterior wall and mid inferior septum were

KEYWORDS Cardiac-only Timothy syndrome; Timothy syndrome; Hypertrophic cardiomyopathy; Long QT syndrome; L-type voltage-gated calcium channel
(Heart Rhythm Case Reports 2023;9:560–564)

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https://doi.org/10.1016/j.hrcr.2023.05.012

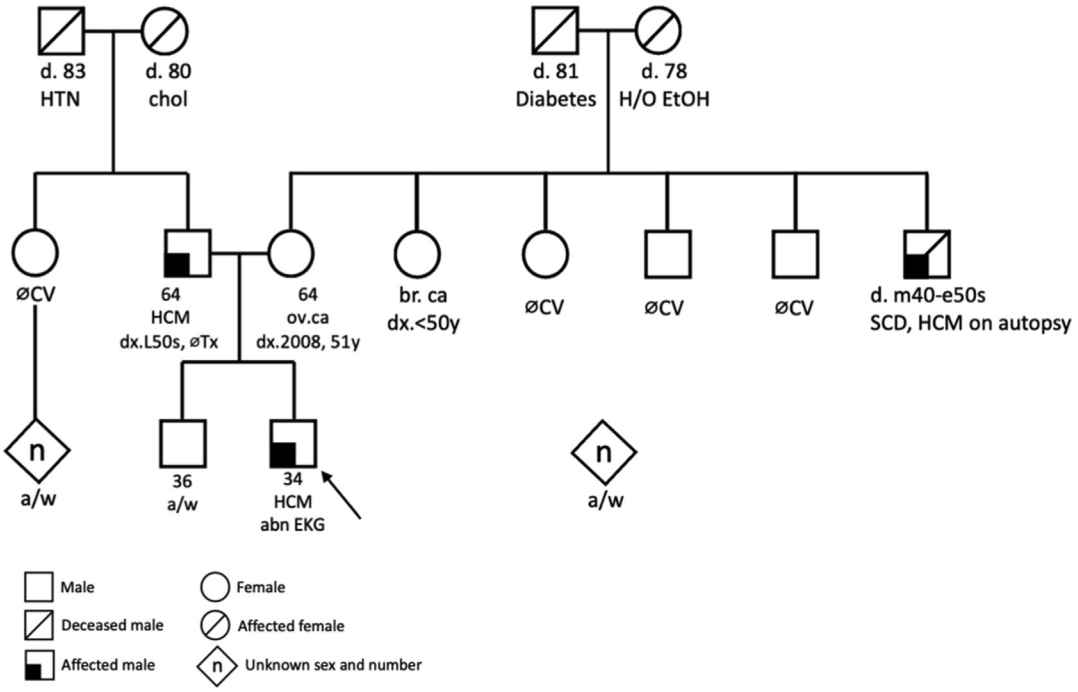

Figure 1 Patient pedigree. Patient is depicted by arrow. ø = not present; a/w = alive and well; br. ca = breast cancer; chol = hypercholesterolemia; CM = cardiomyopathy; CV = cardiovascular disease; dx. = diagnosed; EKG = electrocardiogram; HCM = hypertrophic cardiomyopathy; H/O EtOH = history of alcohol use disorder; ov. ca = ovarian cancer; SCD = sudden cardiac death.

observed. The right ventricle was normal in all measurements. An exercise echocardiography stress test (Figure 2B) exhibited a baseline sinus bradycardia with junctional and ectopic atrial complexes during pre-exercise and recovery ECGs. Manual QT/QTc measurements showed values of 525/509 ms at rest, 320/497 ms during exercise, 380/455 ms at 1-minute recovery, and 480/518 ms at 5-minutes recovery. The patient had adequate exercise capacity with no evidence of ischemia. Doppler-measured left ventricular outflow tract gradient was 41 mm Hg at rest, rising to 143 mm Hg at peak stress. Several ECGs over the following year showed sinus bradycardia of 44 beats per minute, PR interval 180 ms, QRS duration 92 ms, QTc 466–562 ms, and LVH with nonspecific anterior J-point elevation ST-segment abnormalities (Figure 2A and Supplemental Figure 1).

Given the familial history of HCM, we performed a genetic evaluation using an Invitae Arrhythmia and Cardiomyopathy Comprehensive Panel of 157 genes. Results showed a pathogenic variant in the *CACNA1C* gene (c.1553G>A, p.R518H) heterozygous (Figure 3). He also has a heterozygous pathogenic variant in GAA (32-13T>G [intronic]) that is considered pathogenic owing to its association with late-onset Pompe disease when present in the homozygous state, but this specific genetic variant is not expected to cause pathology in the heterozygous state. Following the results of the genetic testing, the patient discontinued use of metoprolol succinate and began a regimen of verapamil 80 mg every 8 hours that was well tolerated. Although the patient has a class IIa indication for an implantable cardioverter-defibrillator implant, he has declined this treatment. Upon follow-up, the patient remains asymptomatic and still exercises without limitation. His last episode of syncope was more than 26 months ago. He has tolerated verapamil well and noted continued bradycardia. We recommended each first-degree relative be screened for the *CACNA1C* mutation, since this is an autosomal condition. After disclosure of his diagnosis to his family members, they have declined to pursue genetic testing, and none have reported symptoms of HCM despite leading active lifestyles. Genetic counseling for future family planning was done, including discussion of preimplantation genetic testing with in vitro fertilization with any potential partners to mitigate transmission of this mutation.

Discussion

TS is a very rare disease, typically diagnosed in childhood, resulting in early mortality. It was first described in 1992 and named after Katherine Timothy, a research coordinator who identified the disease's hallmark features and responsible mutation. Manifestations in neonates include fetal bradycardia and 2:1 atrioventricular block owing to extreme prolongation of the QT interval (QTc >500 ms). It is associated with syndromic extracardiac abnormalities such as syndactyly and autism spectrum disorders.[4,5] TS is usually caused by sporadic mutation of *CACNAIC*, which causes dysfunction in the alpha-1C subunit of L-type calcium channels.[2,3] Interestingly, depending on the gain- or loss-of-function nature of the variation, this gene has been associated with other syndromes like nonsyndromic long QT syndrome

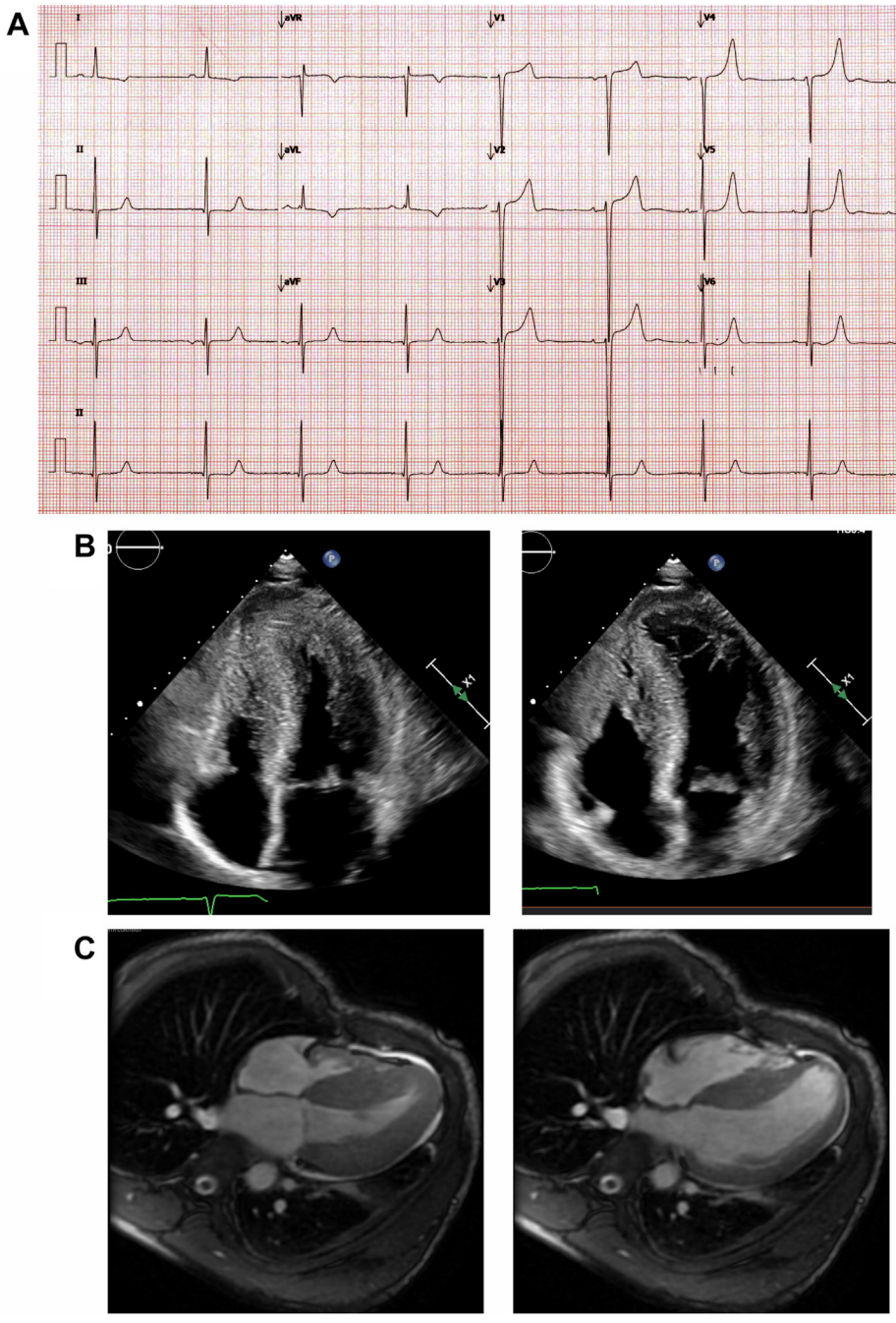

Figure 2 Clinical cardiac testing. **A:** An electrocardiogram showing sinus bradycardia with a QT interval of 562–590 ms that was manually corrected to 480–490 ms. **B:** Echocardiographic apical 4-chamber view in end-systole (left) and end-diastole (right) demonstrating markedly hypertrophied septum. **C:** Magnetic resonance perfusion imaging (without contrast) in end-systole (left) and end-diastole (right) demonstrating septal hypertrophy.

8, short QT, and Brugada syndrome. It has been proposed that pathogenic variations in the *CACNA1C* gene may be the fifth most common cause of LQTS.[6] Furthermore, TS itself has a mosaic of presentations, depending on the missense variant and alternative splicing involved, like at exon 8 and 8A, including TS type 1, TS type 2, and atypical TS.[3,7] Here we present a case of another TS variant called cardiac-only Timothy syndrome or nonsyndromic Timothy syndrome. COTS lacks the extracardiac manifestations of TS but presents with LQTS (albeit with shorter QTc intervals than traditional TS), HCM, septal defects, and sudden cardiac death. Our patient's specific genotype, p.Arg518His, is one of only 3 genetic variants associated with COTS, including R518C and G1911R.[1] The substitution of histidine for arginine at residue 518 resides in the second voltage-sensing domain of the voltage-gated calcium channel (Figure 3). This is associated with a reduced peak current density, a depolarizing shift of inactivation, a hyperpolarizing shift in activation, and increased window current. Perhaps most significant is that impaired inactivation resulted in a sustained

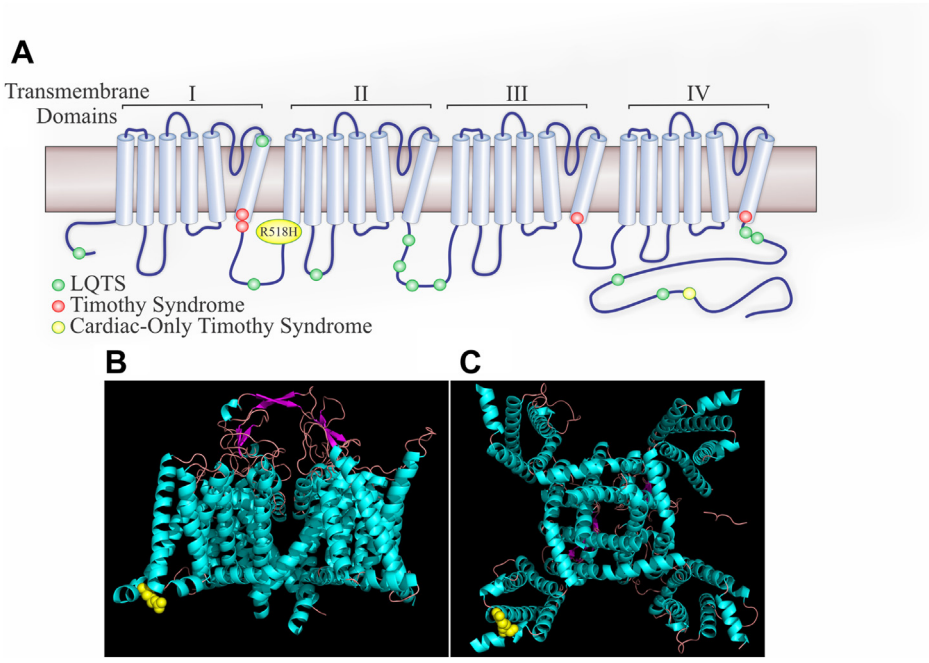

Figure 3 Overview of cardiac L-type calcium channel protein. **A:** Schematic representation of the channel protein with domains embedded in the membrane and location of known pathogenic variants. Red symbols are mutations associated with Timothy syndrome (TS), green symbols show variants associated with isolated QT prolongation, and yellow symbols are variants associated with incomplete TS phenotype. **B:** Side view and **C:** intracellular view of a proposed protein structure of the Cav1.2 protein based on structure of Cav1.1. The R518 residue is highlighted in yellow. Proposed structure generated with AlphaFold.[12]

or late inward calcium that is likely to most impact cardiomyocyte repolarization and prolongation of the QT interval. Simultaneous loss and gain of function in a channel necessary for cardiac excitation and contraction coupling may lead to ventricular hypertrophy and dysfunction owing to complex dysregulation of cardiac calcium handling. For example, chronic internal calcium overload has been associated with impaired systolic and diastolic dysfunction eventually leading to heart failure, which may be evidenced by our patient's reduced left ventricular ejection fraction.[8]

Even among patients with HCM, COTS-associated genetic variations are exceedingly uncommon.[1,9] Given the rarity of this condition, no evidence-based guidelines exist. In 1 case report of COTS with peripartum cardiomyopathy, Larrañaga-Moreira and colleagues[10] maintained a QTc $<$500 ms by administering beta-blockers and avoiding QT-prolonging agents. However, if the root cause of the patient's cardiomyopathy and LQTS is an overactive calcium channel, theoretically, inhibition with calcium channel blockers would be beneficial. This idea is supported in a pluripotent stem cell model of HCM that demonstrated mitigation of cellular hypertrophy by L-type calcium channel blockers.[11] As a result, we transitioned therapy from beta-blockers to verapamil. Additionally, mexiletine and ranolazine have been shown to shorten repolarization by blocking the late sodium current, I_{Na}, and may be considered in the future, if needed.[6]

Conclusion

In patients presenting with both HCM and LQTS, genetic testing is indicated to uncover potential channelopathies. Discovering the pathology and understanding the functional impairment can aid treatment. Our patient presented with history of HCM, LQTS, and syncope for years before he was referred to cardiogenetics. With the diagnosis of COTS, we were able to switch our patient from beta-blockers to calcium channel blockers and manage his symptoms. Given the extraordinary rarity of this condition, there is a paucity of best practices for management of this condition, but he is tolerating the calcium channel blockers well.

Funding Sources: There was no funding for this project.

Disclosures: The authors have nothing to disclose.

Appendix

Supplementary Data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrcr.2023.05.012.

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