Early-onset cardiac arrest, prolonged QT interval, and left ventricular hypertrophy: Phenotypic manifestations of a pathogenic de novo calmodulin variant

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Introduction

Calmodulin (CaM) is a calcium sensor and signal transducer involved in many cellular processes and is ubiquitous in the human body. It is encoded by 3 unique genes, *CALM1, CALM2, and CALM3*, all functional and encoding the same protein. Between 2013 and 2015, missense variants in *CALM* genes were related to different cardiac phenotypes, including long QT syndrome (LQTS), catecholaminergic ventricular tachycardia (CPVT), a combination of both LQTS and CPVT, and even idiopathic ventricular fibrillation. Given the complex phenotypic spectrum, these diseases were named calmodulinopathies. In our case report, we describe a case of a 17-month-old boy who presented with an out-of-hospital cardiac arrest and was diagnosed with both LQTS and left ventricular hypertrophy. The genetic study confirmed the presence of a missense variant in the *CALM2* gene (c.293A>T, p.N98I). Interestingly, the patient also developed severe neurobehavioral impairment. Therefore, this report provides a long-term follow-up of a unique clinical spectrum of LQTS, left ventricular hypertrophy, and neurologic abnormalities, a phenotypic combination that has not been previously reported in the context of *CALM* variants.

KEY TEACHING POINTS

- Even though *CALM* variants are not a common cause of long QT syndrome or catecholaminergic ventricular tachycardia, they should nevertheless be considered in the context of a severe or early-onset disease.
- The presence of multiple cardiac phenotypes in combination with hypertrophic cardiomyopathy are a novel finding that should be considered.
- This case report highlights that the combination of neurologic disorders like attention deficit hyperactivity disorder and dyslexia could be part of the calmodulin phenotype.

Case report

A 17-month-old boy presented with an out-of-hospital cardiac arrest. Prior to his cardiac arrest, he was completely well and was achieving his developmental milestones. He was found apneic and unconscious in bed and basic cardiopulmonary resuscitation was commenced by his parents. Following the arrival of the paramedic team, ventricular fibrillation was identified, and he was defibrillated twice, with return of spontaneous circulation and sinus rhythm. During cardiac resuscitation, 2 doses of intravenous adrenaline were given, with no further inotropic support required during subsequent intensive care. He was mildly acidotic (pH 7.16, lactate 0.9 mmol/L) on arrival at the hospital.

Twelve-lead electrocardiograms (ECGs) consistently showed a prolonged QT interval of over 600 ms after Bazett correction (Figure 1). Initial cross-sectional echocardiography showed concentric left ventricular hypertrophy with interventricular septal wall thickness of 10 mm (Z-score 3.4) and left ventricular posterior wall thickness of 8 mm

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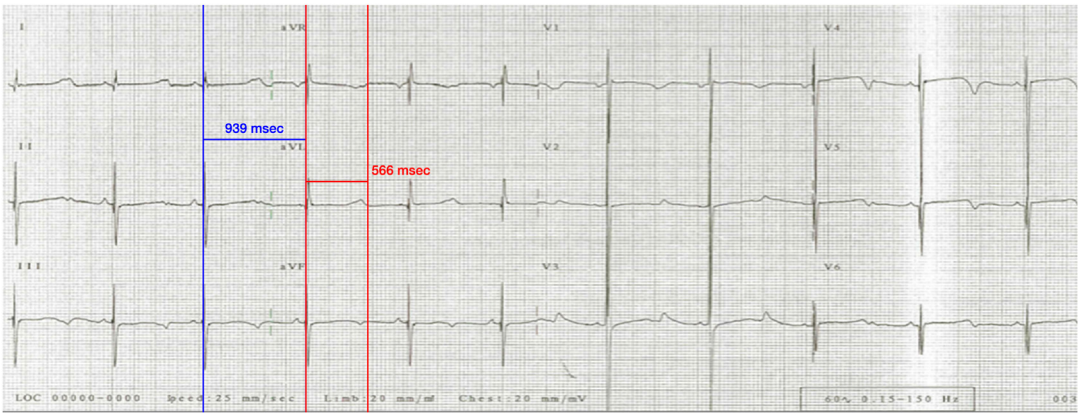

Figure 1 Twelve-lead electrocardiogram (ECG) of patient, aged 17 months, after his cardiac arrest. ECG shows sinus arrhythmia at 65 beats/min, with a QT interval of 566 ms and a corrected QT of 584 ms. Note biphasic T waves in inferior leads and chest leads.

(Z-score 3.3). Intravenous esmolol therapy was commenced and no further ventricular arrhythmias were witnessed. He underwent placement of an implantable cardioverter-defibrillator system using epicardial pace/sense leads and a subpleural defibrillator electrode. Intravenous esmolol was converted to oral propranolol at a dose of 1.5 mg/kg/dose 3 times a day.

He appeared to make a complete neurological recovery, and a brain magnetic resonance imaging (MRI) post arrest showed no abnormalities. Initial genetic analysis of the common LQT-susceptibility genes (*KCNQ1, KCNH2, SCN5A, KCNE1,* and *KCNE2*) did not identify any pathogenic variants. Extended testing identified a variant in the *CALM2* gene (c.293A>T, p.N98I), which encodes for CaM. This missense variant affected a highly conserved residue and was not seen in the Genome Aggregation Database (gnomAD). In silico tools have predicted this variant to be deleterious and damaging. There was no family history of note and cardiac screening on his parents showed normal ECGs and echocardiograms. The *CALM2* variant was not identified in either of them. According to the American College of Medical Genetics and Genomics (ACMG) criteria, this variant would be classified as "likely pathogenic" (PM1, PM2, PM5, PM6, PS3, PP3). His parents did not have any more children.

During his follow-up, his medication was changed from propranolol to nadolol at 1 mg/kg/dose twice a day, and the patient did not experience any other major cardiac events.

At 5 years of age, the patient started to manifest learning difficulties and was diagnosed with attention deficit hyperactivity disorder (ADHD) and dyslexia.

After a follow-up time of 8 years, his corrected QT interval remains prolonged, consistently over 500 ms (Figure 2), and his echocardiogram continues to demonstrate persistent left ventricular hypertrophy (interventricular septal wall thickness 12 mm with a Z-score of 3.65 and left ventricular posterior wall thickness 12 mm, Z-score 4.71) with normal systolic function (fractional shortening 34%) and an ejection fraction of 81% (Figure 3).

Discussion

CaM is a calcium sensor and signal transducer involved in many cellular processes and is ubiquitous in the human body. It is encoded by 3 unique genes, *CALM1*, *CALM2*, and *CALM3*, which are all expressed in the heart throughout life.[1] *CALM* is completely conserved in the human species. Pathogenic variants exert a strong dominant effect, with only 1 mutant allele, out of 6 *CALM* alleles, needed to result in a significant phenotype. The identified variant is thus highly likely to be pathogenic and causative of the cardiac phenotype.

CALM variants have been associated with proarrhythmic risk resulting in cardiac arrest and sudden death, with distinct clinical phenotypes. *CALM1* and *CALM2* variants were initially described in infants with recurrent cardiac arrest, all of whom exhibited a severe cardiac phenotype of recurrent cardiac arrest in the first year of life with a corrected QT interval of greater than 600 ms.[2] *CALM1*, *CALM2*, and *CALM3* variants have subsequently been reported in children up to 9 years old with LQTS.[3–6] *CALM1* variants were also identified in cases of idiopathic ventricular fibrillation and stress-induced polymorphic ventricular arrhythmia akin to CPVT.[7] It is thought that specific *CALM* variants result in differing phenotypes of LQTS and CPVT owing to divergent effects on the various molecular targets.

The IK_s potassium channel is formed by the assembly of *KCNQ1* and *KCNE1* subunits and the associated IK_s current is an important part of cardiac repolarization.[8] CaM binding to *KCNQ1* is essential for correct channel folding and assembly.[9] Thus loss of CaM function can result in a prolonged QT interval. *CALM* variants are also proposed to contribute to QT prolongation by impaired calcium (Ca)-dependent inactivation of the L-type calcium channel $Ca_v1.2$, leading to an excess L-type calcium current during phase 3 of the cardiac action potential.[6,10]

CaM interacts with the ryanodine receptor (RyR2) directly and via Ca/CaM-dependent protein kinase II (CaMKII) to regulate intracardiac calcium levels. Loss of RyR2 inhibition in the presence of a *CALM* variant results in overactive

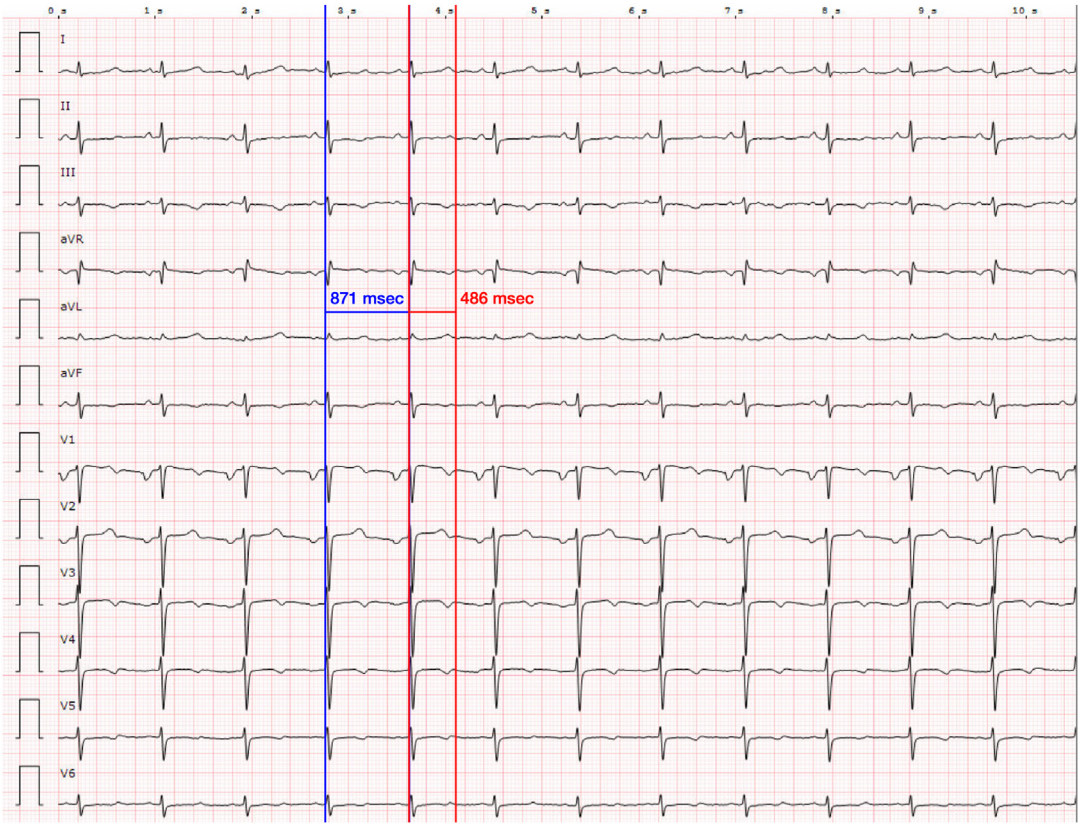

Figure 2 Twelve-lead electrocardiogram (ECG) of patient, aged 10 years. ECG shows sinus arrhythmia at 69 beats/min, with a QT interval measured in lead II of 486 ms and a corrected QT of 520 ms. The negative T waves persist in aVF and also in V_3 and V_6.

calcium channels and subsequent triggered arrhythmia characteristic of CPVT.[11]

Additionally, there is also growing evidence that aberrant sarcoplasmic reticulum calcium release leads to the development of cardiac hypertrophy, and *CALM* variants have been shown in mouse models to result in cardiac hypertrophy and early death.[12] *CALM* variants lead to dysregulation of CaMKII activity and overexpression may lead to cardiac hypertrophy, possibly through increased inhibition of cardiomyocyte apoptosis.[12,13]

Our patient was previously included in the group reported by Makita and colleagues.[3] We found a missense variant in the *CALM2* gene (c.293A>T, p.N98I), which, as far as we know, has not been previously or subsequently reported. Functional studies have demonstrated a significant reduction in calcium-binding affinity to the C-domain. This would be consistent with an impairment in cardiac intracellular calcium signaling, resulting in increased arrhythmia susceptibility.[3] Interestingly, deep phenotyping of our patient exhibited not only a prolonged QT interval but also left ventricular hypertrophy, a phenotypic combination that has not been previously reported in the context of *CALM* variants. Left ventricular hypertrophy can sometimes be seen in infants after a cardiac insult. This usually resolves within months following recovery. Our patient's medical course was brief, being that he was only mildly transiently acidotic and required just 2 doses of intravenous adrenaline. However, the left ventricular hypertrophy has persisted throughout a follow-up period of 8 years, suggesting that the left concentric ventricular hypertrophy is part of our patient's genetic phenotype rather than resulting secondary to cardiac arrest. Unfortunately, since the patient has an epicardial implantable cardioverter-defibrillator in place, further imaging with MRI was not deemed safe. Therefore, myocardial tissue characterization with late gadolinium enhancement has not been performed. In the largest cohort of patients reported by Crotti and colleagues[14] from the International Calmodulinopathy Registry, 18 out of 74 (24%) had structural cardiac abnormalities ranging from patent arterial ducts and septal defects to noncompaction, dilated, and hypertrophic cardiomyopathic phenotypes. In fact, left ventricular hypertrophy was reported in 3 patients, all carrying *CALM2* variants. One of the patients with left ventricular hypertrophy had negative genotyping for other cardiomyopathy-associated genes. We did not carry out additional genotyping for other cardiomyopathy-associated genes. Although our patient may also harbor a variant in a separate cardiomyopathy-associated gene, the finding of persistent left ventricular hypertrophy is most likely to be secondary to his *CALM2* variant, given the observations from the registry and the lack of a significant family history of hypertrophic cardiomyopathy. The evolution of our patient's myocardial phenotype of stable concentric left ventricular hypertrophy with preserved ventricular function from early onset at 17 months of age over a longitudinal follow-up of

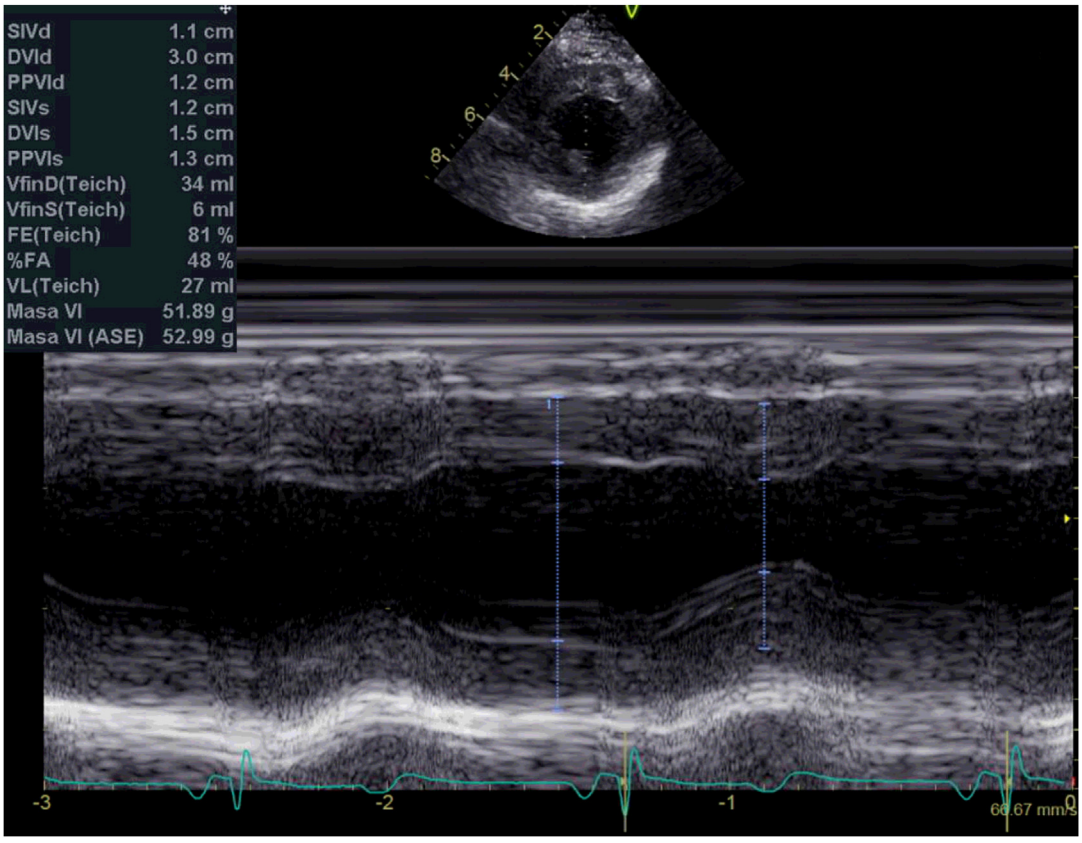

Figure 3 Transthoracic echocardiography of patient, aged 10 years. Left ventricle M-mode of a short-axis view showing thickness of the interventricular septum of 12 mm with a Z-score of 3.65 and left ventricular posterior wall thickness of 12 mm, Z-score 4.71 and left ventricular fractional shortening and ejection fraction.

nearly 10 years is also unique compared to other cases reported in the literature. It is also atypical of more common forms of early-onset infant and childhood hypertrophic cardiomyopathy. Interestingly, the association between *CALM2* variants and increased left ventricle mass has been reported in neonates, suggesting a role for *CALM2* in determining left ventricular mass. There is, however, no mention of the presence of prolonged QT intervals.[15]

Another important aspect of our patient's phenotype is the association of *CALM* variants with neurological abnormalities. In the International Calmodulinopathy Registry, 13 out of 74 (17%) had mild-to-severe neurological impairment, including seizures, development delay, and motor and/or cognitive disability. The authors theorized that in most of the patients who suffered from aborted cardiac arrest, the neurological abnormalities were due to anoxic sequelae; but interestingly, 6 patients had no aborted cardiac arrest but also presented with such features. Therefore, this could be another phenotypic manifestation of *CALM* disorders. Our patient had a brain MRI performed after his cardiac arrest, with no brain abnormalities detected, and his learning difficulties owing to ADHD and dyslexia manifested later on. Although ADHD and dyslexia are relatively common diagnoses in childhood, the ubiquitous presence of calmodulin and its important role in Ca signal transduction may be linked to neurodevelopmental and neurobehavioral impairment. It would, however, require longer-term observation of larger cohorts to make a definitive association.

In summary, CaM's multiple interactions provide a plausible mechanistic basis for developing differential cardiac phenotypes in isolation or combination. Even though *CALM* variants are not a common cause of LQTS or CPVT, they should nevertheless be considered in the context of a severe or early-onset disease, especially in the presence of multiple cardiac phenotypes such as long QT prolongation and polymorphic ventricular tachycardia in combination with hypertrophic cardiomyopathy and neurodevelopmental delay. Further genetic research and careful, accurate phenotyping will likely refine our understanding of the role of *CALM* variants in arrhythmia syndromes.

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