Cardiology in the Young

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Cardiac phenotypic spectrum of *KCNT1* mutations

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Brief Report

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Abstract

We report a 10-month-old girl with *KCNT1* (c1420C > T; p. Arg474Cys, R474C) mutation-associated epileptic encephalopathy, systemic-to-pulmonary artery "collateralopathy", and intermittent QTc prolongation. Spontaneous regression of systemic-to-pulmonary artery collateral-mediated left heart dilation was noted in this patient, a finding which was ominous as it heralded the onset of severe pulmonary hypertension. The structural and electrical phenotypic features of *KCNT1* mutation-associated heart disease, including the novel findings noted in our patient, are discussed in detail.

Case report

We report the case of a 10-month-old Caucasian girl with developmental delay and epileptic encephalopathy requiring multiple anti-epileptic therapies (phenobarbital, vigabatrin, pyridoxine, levetiracetam, and ketogenic diet). She was initially evaluated at 2 months of age for a systolic heart murmur. An echocardiogram was obtained and showed moderate left atrial and left ventricular dilation (Fig 1, Panels A and B). There were no intra- or extracardiac shunts identified and biventricular function was normal. The main and branch pulmonary arteries measured normal in size. Given the unexplained left atrial and ventricular dilation, she subsequently underwent a cardiac CT angiogram which confirmed the echocardiographic findings (moderate to severe left atrial and moderate left ventricular dilation). No atrial or ventricular septal defects or aortopulmonary window were visualised. The coronary artery origins appeared normal. A complex network of small systemic-to-pulmonary artery collateral vessels was visualised bilaterally in the paraesophageal and perihilar regions. A few of these collateral vessels originated from the descending aorta but it was difficult to definitively ascertain complete source and drainage of the entire vascular networks (Fig 2). The left heart enlargement was therefore attributed to systemic-to-pulmonary artery collateral mediated left-to-right shunting. Of note, the patient had undergone an echocardiogram at 2 weeks of age at another centre which showed only a patent foramen ovale and no evidence of left heart enlargement.

A brain MRI scan with spectroscopy, obtained at 2 months of age, showed delayed myelination for age with a thin corpus callosum. Non-specific small foci of susceptibility in the cerebellar hemispheres reflecting chronic microhaemorrhages or mineralisation were noted. MR spectroscopic findings were within normal limits for her age. A video electroencephalographic study obtained during awake and sleep state at 3 months of age showed abnormal background activity with striking discontinuity, abundant independent multi-focal epileptiform discharges, and numerous electroclinical seizures. In addition, the study revealed multiple diffuse epileptic seizures which were clinically characterised as asynchronous tonic seizures and isolated epileptic spasms. The findings were consistent with a severe early infantile encephalopathy, such as Ohtahara syndrome. Within 1 month, the electroencephalographic background became more continuous, but the patient developed migrating focal seizures occurring multiple times daily. Ultimately, with a combination of anti-epileptic medications and ketogenic diet, the seizures were reduced to 0–5 isolated, brief focal seizures arising from multiple regions.

An epilepsy panel (Invitae, San Francisco, CA) was obtained and revealed a pathogenic variant in *KCNT1* (c1420C > T; p. Arg474Cys, R474C) which is associated with intractable seizures and severe cognitive and motor impairment. A likely pathogenic variant was identified in the *PNKP* (polynucleotide kinase 3 prime-phosphatase) (MIM 605610) (partial deletion exon 14). The *PNKP* is associated with autosomal recessive early infantile epileptic encephalopathy. However, *PNKP*-related conditions are known to be only caused by the co-occurrence of two pathogenic variants. Variants of unknown significance were identified in *PIGN* (phosphatidylinositol glycan anchor biosynthesis) (MIM 606097) (c2486C > A; p. Ala829Asp) and

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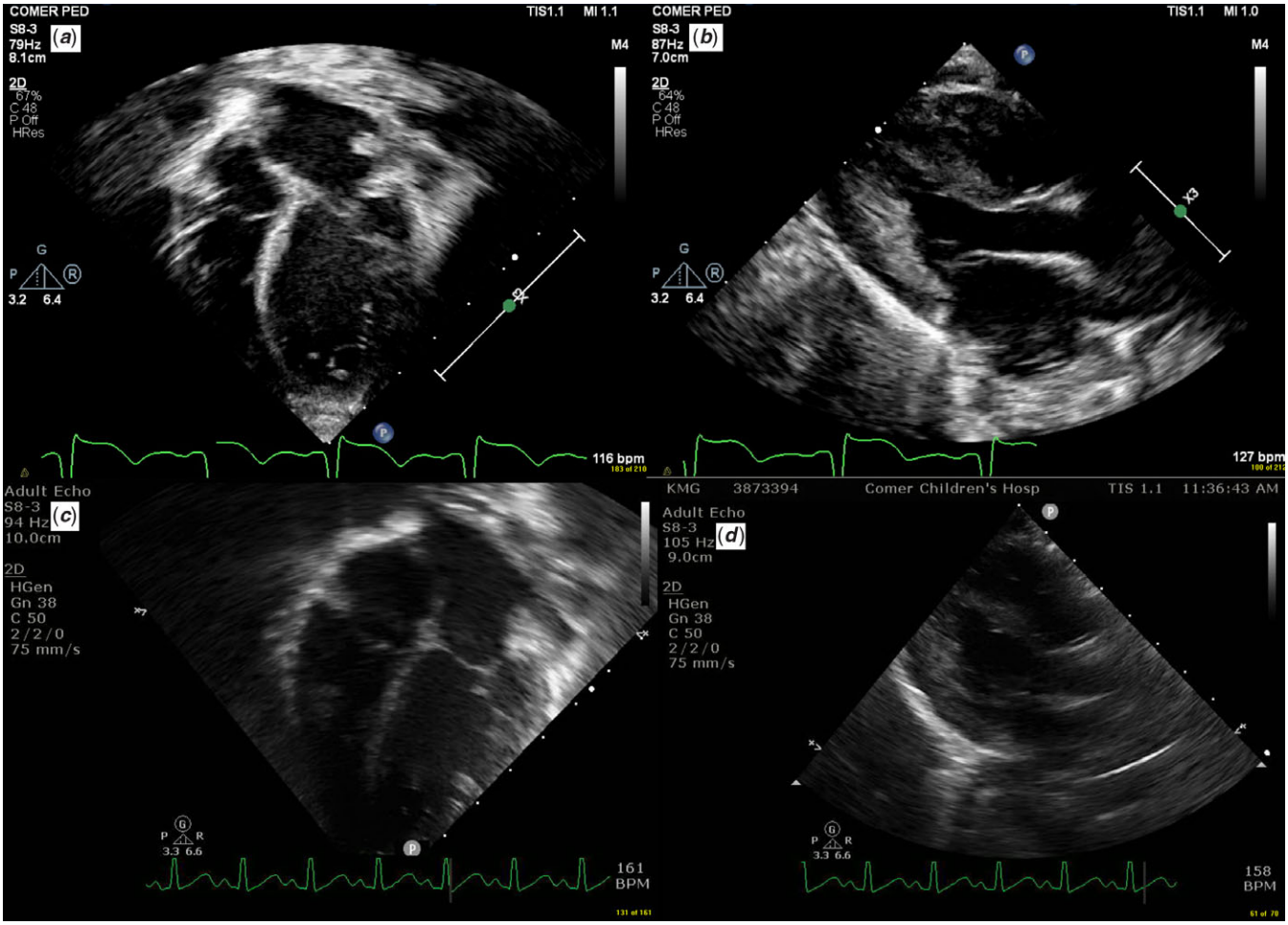

Figure 1. Moderate left atrial and left ventricular dilation (M-mode: left ventricular internal dimension [diastolic] = 2.8 cm, Z score = 3.8) is noted in apical 4-chamber (Panel A) and parasternal long-axis (Panel B) views at 2 months of age. The same views show complete regression of left atrial and left ventricular (M-mode: left ventricular internal dimension [diastolic] = 2.9 cm, *Z* score = 2.0) enlargement at 7 months of age (Panels C and D).

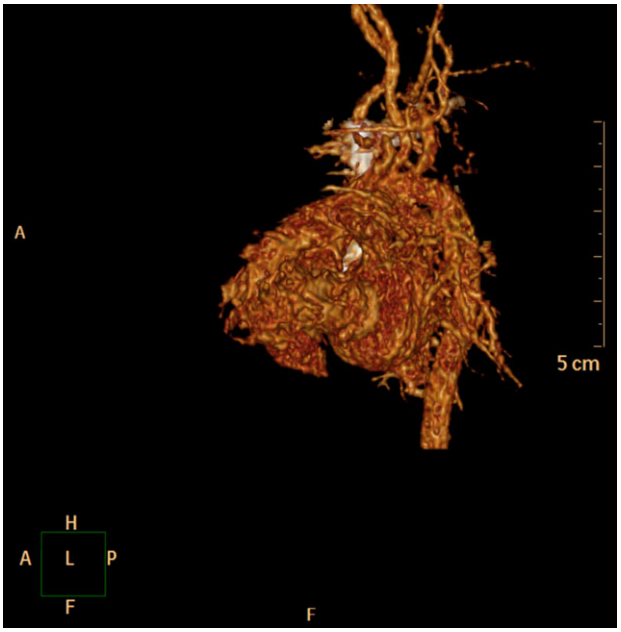

Figure 2. A meshwork of small systemic-to-pulmonary artery collaterals is noted to arise from ascending and descending aorta and arch arteries on this CT angiographic image with 3D reconstruction.

PRRT2 (proline-rich transmembrane protein 2) (MIM 614386) (gain, entire coding sequence, copy number = 3) genes.

Upon follow-up, she was noted to have intermittent prolongation of corrected QT interval (QTc: 450–509 ms) (Fig 3, Panel A) between 5 and 6 months of age. The patient did well until 9 months of age without any tachypnea, cough, or haemoptysis. Serial echocardiograms during this period showed progressive normalisation of left atrial and ventricular sizes (Fig 1, Panels C and D). The most recent echocardiogram, however, has shown severe pulmonary hypertension (Fig 3, Panel B). Her seizures are well controlled on the current therapeutic regimen (<5 seizures per day) but she does have marked developmental delay. Recent electrocardiograms (over the past 2 months) have shown a normal corrected QT interval. She has been started on pulmonary vasodilator therapy and is being closely monitored.

Discussion

KCNT1 (also known as SLACK, SLO2.2, or KCa4.1) gene, which is strongly conserved over evolution, encodes a sodium-activated potassium (K_{Na}) channel which is widely expressed in the nervous system where it contributes to the slow hyperpolarisation that follows repetitive firing of neurons. *KCNT1*, therefore, regulates the rate of burst firing and enhances the accuracy with which action potentials lock to incoming stimuli. In addition,

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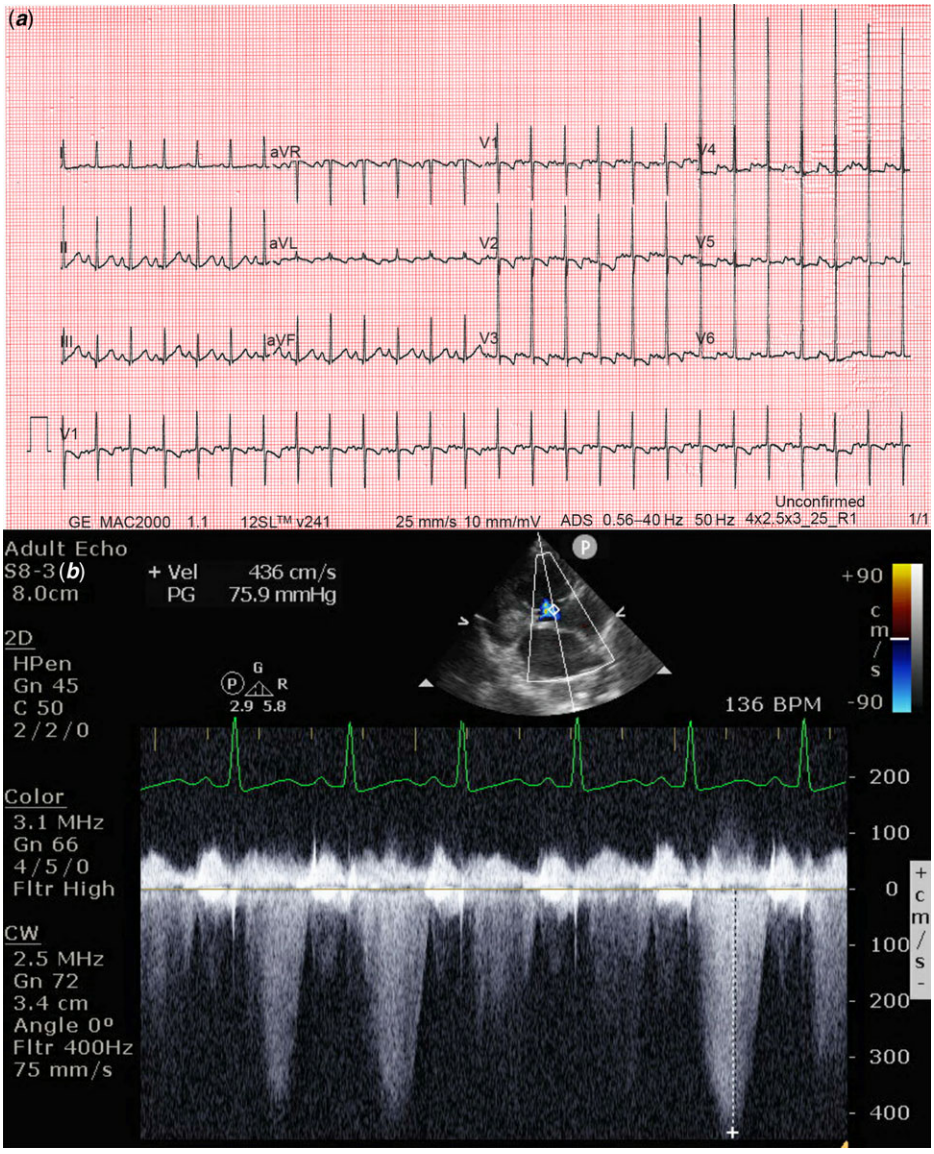

Figure 3. Borderline prolonged corrected QT interval is noted on this electrocardiogram (Panel A). Continuous wave Doppler interrogation of the tricuspid regurgitation jet reveals severe elevation in right ventricular pressure (Panel B).

K_{Na} channels also play a role in protecting cells from injury under ischemic conditions.[1,2]

KCNT1-encoded K_{Na} channel is also expressed in cardiac myocytes where its precise role has not been defined.[2,3] However, antiarrhythmics, such as quinidine, clofilium tosylate, and bepridil, have been found to inhibit K_{Na} channel suggesting that this channel may play a role in regulation of cardiac electrical activity and arrhythmogenesis.[3]

KCNT1 (c1420C > T; p. Arg474Cys, R474C) variant, which affects the carboxy-terminus regulator of potassium (RCK) domain of the protein,[4] has previously been reported as a *de novo* change in six individuals with severe infantile-onset epilepsy syndromes.[5–7] This variant has also been reported in a 2-day-old Japanese girl with epilepsy, heart failure, and systemic-to-pulmonary artery collaterals who died of massive haemoptysis despite several catheter-based interventions on collaterals.[8] This substitution occurs at a position which is conserved across the species and was not observed in approximately 6500 individuals of European and African American ancestry in the NHLBI Exome Sequencing Project, indicating it is not a common benign variant in these populations. Moreover, *in silico* analysis predicts this variant is probably damaging to the protein structure/function. Finally, alternative missense variants at the same residue (c.1421 G > A; p.R474H) or other missense variants in the nearby residues (c.1420 C > T; p.R474C) (R477T) have been reported in association with *KCNT1*-related disorders,[1,7,9] supporting the functional importance of this region of the protein.

KCNT1 mutations have been associated with a broad range of neurological phenotypes such as malignant migrating partial seizures in infancy, autosomal-dominant nocturnal frontal lobe epilepsy, leucoencephalopathy, and early-onset epileptic encephalopathy including Ohtahara and West syndromes.[1,4] Most of these epilepsy syndromes have onset early in infancy and are frequently characterised by refractoriness to anti-epileptic medications and poor outcome.[7,10]

Less is known about the cardiac effects of *KCNT1* mutations. In 2017, Kawasaki *et al* reported three Japanese infants with *de novo* *KCNT1* mutations who had bilateral profuse systemic-to-pulmonary artery collaterals which originated from aortic arch, descending aorta, and subclavian arteries.[8] Interestingly, one of these three patients carried the same missense mutation as our patient and another had a missense mutation at an adjacent residue

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(c.1420 C > T; p.R474C). Two of the three reported infants had heart failure symptoms and all three had left heart enlargement and several episodes of haemoptysis which recurred despite multiple catheter-based interventions on collaterals. More importantly, haemoptysis was reported to be the cause of death in two of these patients. Since then, a few other patients have been found to have systemic-to-pulmonary artery collaterals in association with *KCNT1*-associated epilepsy (verbal communication from a colleague at the Children's Hospital of Philadelphia), but the exact prevalence and the natural history of systemic-to-pulmonary "collateralopathy" in these patients remains unknown. These findings are intriguing as systemic-to-pulmonary artery collaterals are typically seen at birth in complex CHDs such as tetralogy of Fallot with pulmonary atresia and can be acquired in those with single-ventricle physiology. In tetralogy of Fallot with pulmonary atresia, these collateral vessels augment pulmonary blood flow and may be the sole source of pulmonary blood flow to certain segments of the lungs but are considered an unreliable source as they can undergo dynamic changes, including stenosis and complete involution. Primary cardiac disease due to systemic-to-pulmonary artery collaterals, as seen in patients with *KCNT1* mutations, has not been reported before.

Even though the data are sparse, the clinical course and the echocardiographic findings in our patient suggest that spontaneous regression of systemic-to-pulmonary artery collateral-mediated left heart dilation in carriers of *KCNT1* mutations may be an indicator of elevated pulmonary vascular resistance and pressures. Whether all carriers of *KCNT1* mutations should be screened for collateral-associated heart disease and the optimal modality for such screening (echocardiography versus CT angiography or cardiac MRI) remains unknown. Once the collaterals are identified, the risk of life-threatening complications such as haemoptysis or pulmonary hypertension, and optimal timing for intervention are important questions that beg an answer.

Other vascular abnormalities such as an arteriovenous fistula between the hepatic artery and the left portal branch have also been reported in these patients.[7] These clinical findings suggest that *KCNT1*-encoded K_{Na} channel may play a yet unknown role in cardiovascular angiogenesis.

In addition to structural abnormalities such as "collateralopathy", *KCNT1* mutations have also been associated with electrical abnormalities. A high incidence of sudden unexpected death has been reported in these patients, suggesting an underlying propensity to malignant arrhythmias.[7] Specific arrhythmogenic phenotypes have been reported in some patients. A patient with Brugada syndrome leading to arrhythmogenic syncope was found to have *KCNT1* carboxy terminus c.3317 G > A; pArg1106Gln mutation. An additional patient with the same mutation and multi-drug refractory seizures has also been reported.[4,11,12] This patient was diagnosed at 12 years of age and has had a normal 24-hour Holter evaluation and has done well from a cardiac standpoint. An unspecified cardiac arrhythmia has been reported in a young patient with familial *KCNT1* c.2782 C > T; p. Arg928Cys mutation.[13] Our patient had intermittent prolongation in corrected QT interval despite not being on any QTc prolonging medications and normal serum potassium, calcium, and magnesium concentrations. This finding has previously not been reported in *KCNT1* mutations carriers.

Quinidine, a class IA antiarrhythmic drug, has been shown to reverse *KCNT1*-encoded K_{Na} channel over activity *in vitro*.[14] These encouraging *in vitro* findings have led to evaluation of quinidine in patients with *KCNT1*-associated epilepsy syndromes with mixed results. While some patients have shown improvement, evidence for a convincing neurological response is lacking in the majority. Serious adverse effects such ventricular arrhythmias have, however, been reported with quinidine use. Of note, all of these trials are limited by a small sample size which makes drawing any conclusions difficult.[15–17] The effects of quinidine on cardiovascular features of *KCNT1* mutations have not been systematically evaluated.

In summary, *KCNT1* mutations, which encode a gain-of-function K_{Na} channel, are associated with a unique systemic-to-pulmonary artery collateral-mediated heart disease or "collateralopathy" which is characterised by a net left-to-right shunt leading to left heart enlargement. This "collateralopathy" can clinically present as heart failure, life-threatening haemoptysis, or pulmonary hypertension. Though only a handful of patients have been reported, the natural history of *KCNT1* mutation-associated "collateralopathy" appears variable with most of the reported patients experiencing an unrelenting course with recurrent episodes of haemoptysis despite multiple catheter-based interventions. As seen in our patient, spontaneous regression of systemic-to-pulmonary collateral-mediated left heart dilation is certainly possible in *KCNT1* mutation carriers; however, these patients should be carefully monitored for pulmonary hypertension. It is possible that the reported patients represent the "tip of the iceberg" and milder subclinical forms of this condition with left heart enlargement on imaging but no clinical symptoms also exist. *KCNT1* mutations are also associated with a higher risk of sudden death suggesting pre-disposition to malignant arrhythmias. The precise substrate leading to this increased risk has not been defined but may include cardiac phenotypes, such as Brugada syndrome and possibly prolonged corrected QT interval. Further studies are needed to systematically evaluate the cardiovascular effects of *KCNT1* mutations.

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Conflict of Interest. None.

Ethical Statement. Informed consent was obtained from all individual participants included in the report. This report does not include any human or animal experimentation.

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