

Case report

Neurologic presentation unmasks arrhythmogenic channelopathy: KCNH2 variant Long-QT syndrome managed with subcutaneous implantable cardioverter-defibrillator. A case report

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Conflicts of interest

This clinical case received first prize in the clinical case competition at the 2nd International Electrophysiology Congress of the National Cardiovascular Institute (INCOR) 2026 and in the cardiology residents' clinical case competition of the Peruvian Society of Cardiology (SOPECARD) 2026.

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ABSTRACT

A previously healthy 10-year-old boy developed febrile seizure-like episodes after an appendectomy, which were diagnosed as epilepsy despite a normal electroencephalogram. He later presented with dyspnea and palpitations and was prescribed propafenone for frequent premature ventricular complexes. The electrocardiogram showed a markedly prolonged QTc interval of 550 ms with a notched T wave in lead V2. Phenytoin and propafenone were discontinued, and propranolol was initiated, but QTc prolongation persisted. The combination of severely prolonged QTc, characteristic T-wave morphology, and absence of structural heart disease redirected the diagnosis toward a repolarization channelopathy; genetic testing confirmed long-QT syndrome type 2 due to a pathogenic KCNH2 c.1814C>T variant. β -blocker therapy was optimized, QT-prolonging triggers were avoided, and a subcutaneous implantable cardioverter-defibrillator was implanted. Cascade genetic screening identified no additional KCNH2 carriers. One variant-negative sister had frequent idiopathic right ventricular outflow tract premature ventricular complexes and was referred for catheter ablation.

Keywords: Long QT Syndrome; Death, Sudden, Cardiac; Defibrillators, Implantable (Source: MeSH-NLM).

RESUMEN

Una presentación neurológica desenmascara una canalopatía arritmogénica: síndrome de QT largo asociado a una variante en KCNH2 tratado con desfibrilador automático implantable subcutáneo. Reporte de caso.

Varón de 10 años, previamente sano, con crisis epileptiformes en contexto febril tras apendicectomía, inicialmente catalogadas como epilepsia pese a un electroencefalograma normal. Evolucionó con disnea y palpitaciones; recibió propafenona debido a extrasístoles ventriculares. El electrocardiograma evidenció un intervalo QTc de 550 ms con T melladas en precordiales y Holter sin taquiarritmias; se suspendieron fenitoína y propafenona, y se inició propranolol; sin embargo, el intervalo QTc persistió prolongado. La combinación de QTc severamente prolongado y ausencia de cardiopatía estructural reorientó el diagnóstico a canalopatía de repolarización; el estudio genético confirmó síndrome de QT largo (SQLT) tipo 2 por mutación KCNH2 c.1814C>T. Se optimizó el betabloqueo, se indicó evitar condiciones que prolonguen el QT y se implantó un desfibrilador automático implantable subcutáneo. El tamizaje genético en cascada no identificó portadores adicionales de KCNH2. Una hermana no portadora presentó complejos ventriculares prematuros frecuentes con morfología de bloqueo de rama izquierda y eje inferior, compatibles con origen idiopático en el tracto de salida del ventrículo derecho, por lo que fue referida para ablación con catéter del foco ectópico.

Palabras clave: Síndrome de QT Prolongado; Muerte Súbita Cardíaca; Desfibriladores Implantables (Fuente: DeCS-BIREME).

Introduction

Congenital long-QT syndrome (LQTS) comprises a group of uncommon inherited disorders of cardiac repolarization defined by prolongation of the QT interval on surface electrocardiography.⁽¹⁾ LQTS confers susceptibility to recurrent syncope and life-threatening ventricular arrhythmias, including torsades de pointes (TdP) and sudden cardiac death; these events are typically precipitated by abrupt adrenergic surges, including auditory startle or intense emotional stress.⁽²⁾

The prevalence has been estimated to be at least 1 in 2,000 live births, based on a population-based cohort of approximately 44,000 infants who underwent standardized electrocardiographic screening followed by confirmatory genetic testing; nevertheless, the true prevalence is likely higher because genotype-positive, phenotype-negative individuals were not ascertained.^(1,3) The mean age at first presentation is approximately 14 years, and historical cohort data suggest an annual sudden cardiac death incidence of <0.5% among asymptomatic untreated patients, rising to 5% in those with a history of syncope.^(2,4)

Congenital LQTS results from pathogenic variants affecting cardiac ion channel genes or their regulatory proteins, thereby disrupting channel function and prolonging ventricular repolarization.⁽⁵⁾ Pathogenic variants in more than a dozen genes have been implicated, although the 3 major subtypes—LQTS1 (KCNQ1), LQTS2 (KCNH2), and LQTS3 (SCN5A)—collectively account for approximately 80%–90% of genotype-positive cases.⁽⁶⁾

The clinical importance of timely diagnosis is highlighted by the observation that approximately 13% of cases present with sudden cardiac death; moreover, the syndrome has been implicated in approximately 10% of sudden infant death cases.^(3,7) This entity represents a diagnostic challenge because approximately 10% of cases present with seizure-like episodes that are misclassified as epilepsy, which can delay diagnosis by up to 5 years. This difficulty is compounded by incomplete phenotypic expression, as up to 40% of genotype-confirmed individuals may have a corrected QT interval (QTc) within the conventionally normal range.^(2,8)

We present a 10-year-old boy who initially manifested epileptiform seizures and summarize the diagnostic evaluation that led to the diagnosis, highlighting the value of cardiac genetic testing and subcutaneous implantable cardioverter-defibrillator (S-ICD) therapy.

Case report

A previously healthy 10-year-old boy, conceived by in vitro fertilization and with no family history of sudden cardiac death, was diagnosed with acute appendicitis and underwent appendectomy. During the febrile postoperative period, he experienced 4 syncopal episodes accompanied by seizure-like

motor activity with generalized tonic-clonic features and was presumptively diagnosed with epilepsy, for which phenytoin was initiated despite a normal electroencephalogram during both wakefulness and sleep. Four weeks later, he developed palpitations followed by exertional dyspnea and fatigue, and 2 weeks thereafter his symptoms progressed to presyncope.

Frequent premature ventricular complexes were documented on electrocardiography, and propafenone was prescribed. At follow-up two weeks later, marked QT prolongation was recognized, with a Bazett-corrected QT interval of 550 ms; both phenytoin and propafenone were discontinued, and propranolol was initiated at 0.5 mg/kg twice daily. At our center, cardiac computed tomography and transthoracic echocardiography showed no structural abnormalities (**Videos 1 and 2**). The resting electrocardiogram demonstrated sinus rhythm, T-wave inversion in leads V1 and V3, a notched T wave in lead V2, and a Bazett-corrected QT interval of 550 ms, without evidence of T-wave alternans (**Figure 1**), whereas 24-hour Holter monitoring did not reveal sustained tachyarrhythmias. Moreover, multimodality imaging excluded structural substrates for arrhythmia, including arrhythmogenic cardiomyopathy, sequelae of myocarditis, and congenital heart disease, while normal metabolic, hormonal, and electrolyte profiles ruled out secondary causes of QT prolongation. Taken together, the seizure-like events during fever with a normal electroencephalogram, the persistently prolonged QT interval despite the discontinuation of antiarrhythmic therapy, the characteristic T-wave morphology, and the structurally normal heart redirected the diagnosis toward an inherited repolarization channelopathy.

Based on this overall assessment, the index event was interpreted as probable aborted sudden cardiac death, and the subsequent episodes were considered arrhythmic syncope; 2 occurred in the immediate post-awakening period, whereas the other 2 coincided with fever. Genetic testing identified a pathogenic KCNH2 c.1814C>T (p.Pro605Leu) variant, confirming the diagnosis of long-QT syndrome type 2, refining risk stratification, and guiding subsequent management. For risk stratification and to guide definitive therapy, the validated 1-2-3-LQTS Risk score was applied, yielding an estimated 5-year risk of 9.3%, consistent with high arrhythmic risk. In addition, the heart team considered the possibility that the index event represented a self-terminating aborted sudden cardiac death, further strengthening an already compelling indication for defibrillator therapy based on the patient's overall clinical profile and high arrhythmic risk. Because antitachycardia pacing has limited utility for malignant ventricular arrhythmias in congenital LQTS and preservation of long-term vascular access is particularly important in pediatric patients, an S-ICD was selected over a transvenous system. The S-ICD was subsequently implanted (**Figure 2**), propranolol was uptitrated, avoidance of QT-prolonging drugs and conditions was strongly emphasized, and the family received education regarding emotional and auditory triggers.

The patient subsequently developed a pocket infection without systemic or endocardial involvement, which was managed with complete S-ICD system explantation, antibiotic therapy, and reimplantation two weeks later, followed by an uneventful course. Cascade genetic screening identified no

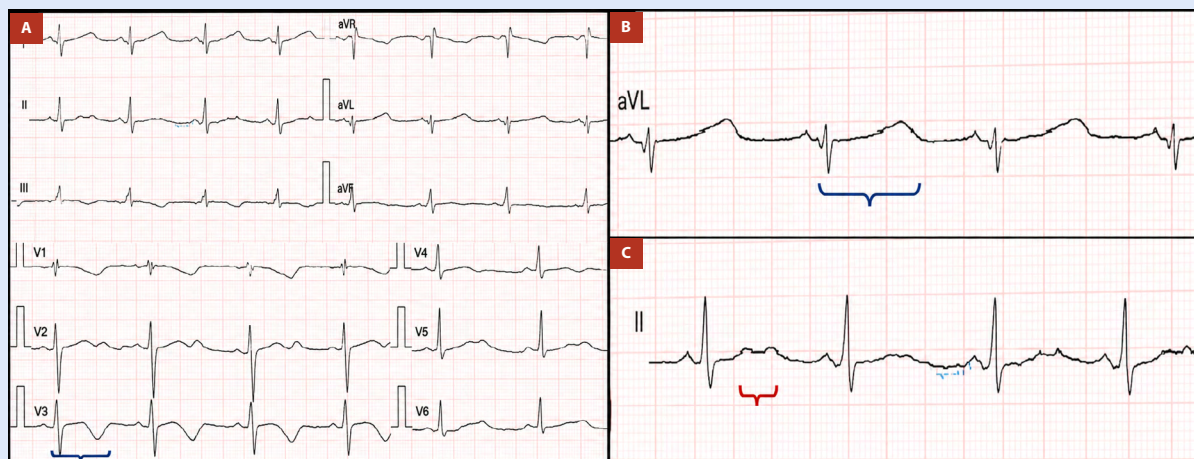


Figure 1. Resting electrocardiogram of the index patient. **A)** Twelve-lead electrocardiogram obtained after 2 months of β -blocker therapy showing sinus rhythm at 68 beats per minute, normal frontal QRS axis, PR interval 140 ms, narrow QRS complexes without pathologic Q waves or voltage criteria for ventricular hypertrophy, T-wave inversion in leads V1 and V3, a notched T wave in lead V2, and marked QT-interval prolongation in lead V3 (blue bracket). **B)** Magnified view of lead aVL (blue bracket) illustrating manual measurement of the QT interval with a Bazett-corrected QTc of 550 ms. **C)** Magnified view of lead D2 (red bracket) highlighting a low-amplitude, notched biphasic T wave with delayed terminal repolarization, a pattern characteristic of long-QT syndrome type 2 (KCNH2).

additional carriers of the familial KCNH2 pathogenic variant (**Figure 3**). One variant-negative sister reported New York Heart Association functional class II exertional dyspnea, fatigue, and asthenia; her electrocardiogram showed frequent premature

ventricular complexes with left bundle-branch-block morphology and an inferior axis, consistent with an idiopathic right ventricular outflow tract origin, and a borderline Bazett-corrected QTc of 460 ms without additional repolarization abnormalities suggestive of

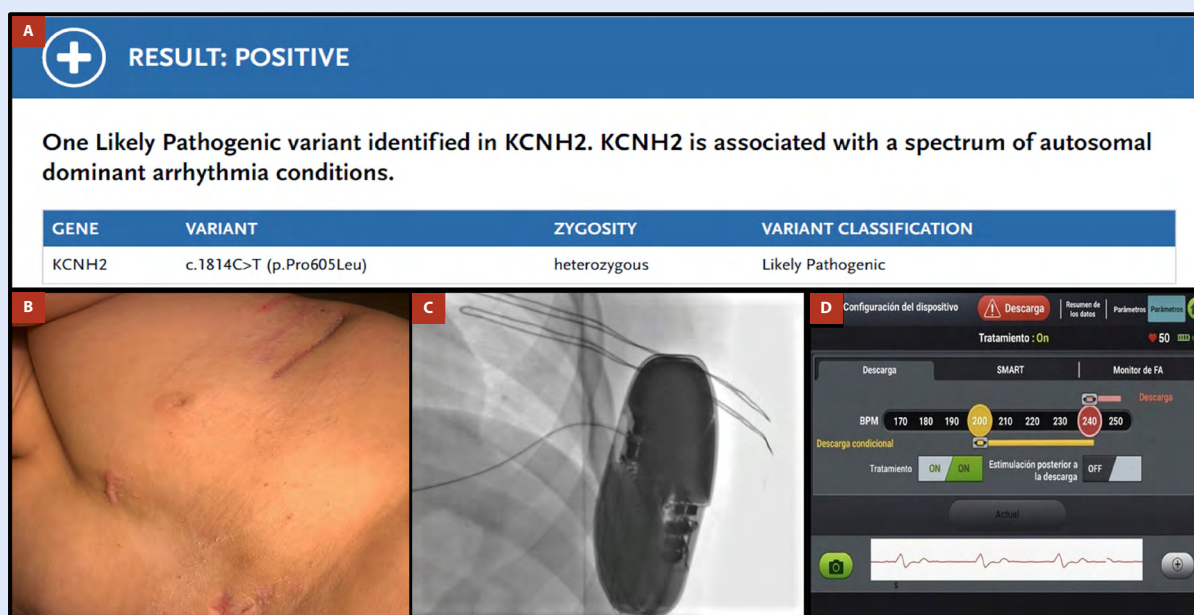


Figure 2. Genetic confirmation of KCNH2-mediated congenital long-QT syndrome type 2 and subcutaneous implantable cardioverter-defibrillator (S-ICD) therapy. **A)** Multigene panel testing for inherited cardiac arrhythmia syndromes (CACNA1C, CALM1–3, KCNE1, KCNH2, KCNJ2, KCNQ1, SCN5A, TRDN) identified a heterozygous KCNH2 exon 7 c.1814C>T (p.Pro605Leu) variant classified as likely pathogenic in a gene associated with autosomal-dominant long-QT syndrome type 2; in this patient, the finding establishes the diagnosis of congenital LQTS2. **B)** Post-reimplantation photograph of the left lateral chest wall demonstrating a well-healed S-ICD generator pocket and subxiphoid lead incision without erythema, swelling, or drainage, indicating complete resolution of the prior pocket infection after reimplantation with a two-incision technique. **C)** Anteroposterior fluoroscopic image of the S-ICD system with the pulse generator positioned in the left lateral thoracic region and the parasternal lead appropriately aligned along the left sternal border. **D)** Device-interrogation screen documenting a conditional shock zone programmed between 200 and 240 beats per minute, a shock zone ≥ 240 beats per minute, absence of recorded or treated ventricular arrhythmias, shock impedance of 85 Ω , and an estimated remaining battery life of 96%.

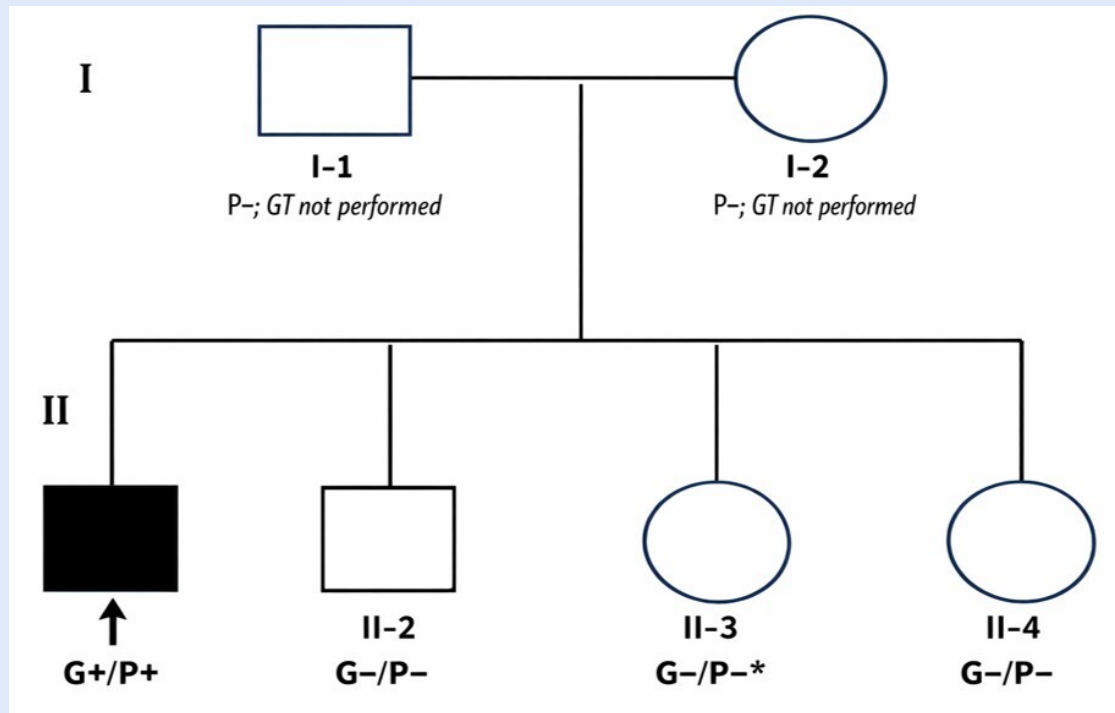


Figure 3. Pedigree of the family of the proband with KCNH2-mediated long-QT syndrome type 2. Squares represent males and circles females; the filled symbol with an arrow indicates the proband (II-1), who is genotype-positive/phenotype-positive (G+/P+) for the familial KCNH2 pathogenic variant and has clinical congenital LQTS type 2. Both parents (I-1, I-2) are phenotype-negative (P-) with normal cardiologic evaluation; genetic testing (GT) was not performed because of limited local availability. Among the siblings, individuals II-2 and II-4 are genotype-negative/phenotype-negative (G-/P-), whereas II-3 is genotype-negative with ventricular ectopy (*), prompting extended electrophysiologic assessment but without electrocardiographic evidence of LQTS. Because parental genetic testing was not available, the mode of inheritance cannot be fully established; the figure underscores the role of targeted cardiogenetic testing and cascade clinical screening in relatives of an index case.

Abbreviations: G+, genotype positive for the familial KCNH2 pathogenic variant; G-, genotype negative; P+, phenotype positive (clinical LQTS); P-, phenotype negative; LQTS, long-QT syndrome; GT, genetic testing; *, ventricular ectopy requiring further evaluation.

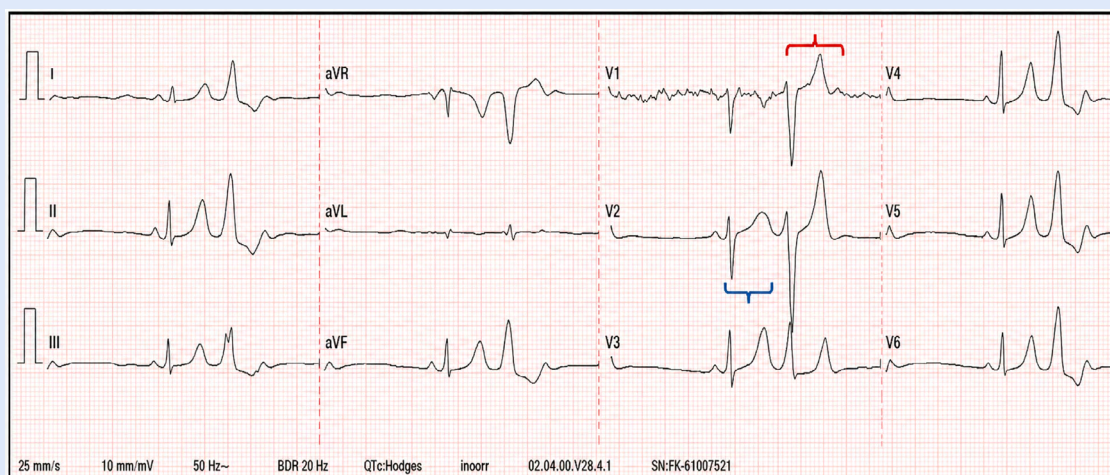


Figure 4. Electrocardiogram of the proband's sister with frequent right ventricular outflow tract ectopy. Twelve-lead electrocardiogram showing sinus rhythm with frequent monomorphic premature ventricular complexes (red bracket) with left bundle branch block morphology and inferior axis, consistent with a right ventricular outflow tract origin. The blue bracket in lead V2 denotes the measured QT interval; the Bazett-corrected QT interval (QTc) is 460 ms, within the borderline range and without repolarization abnormalities suggestive of LQTS2. In this sibling, standardized exercise and standing tests showed no diagnostic QTc abnormality, further lowering the likelihood of congenital LQTS. Genetic testing for the familial KCNH2 variant was negative, and the arrhythmia was classified as idiopathic RVOT premature ventricular complexes refractory to medical therapy, prompting referral for catheter ablation.

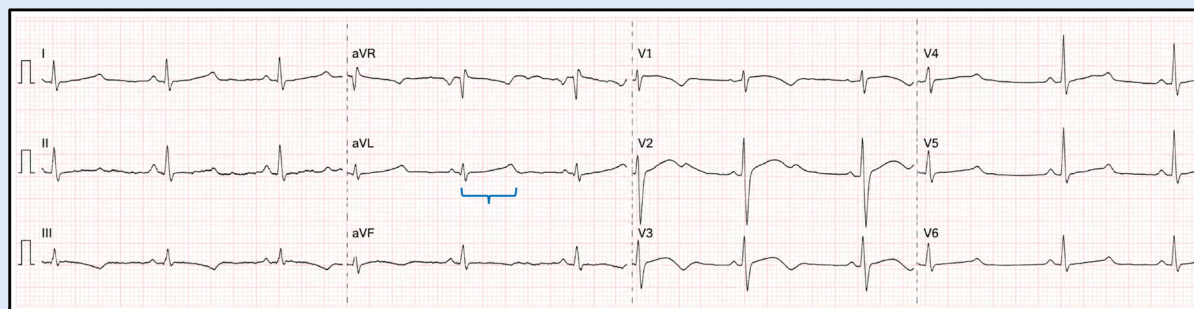


Figure 5. Twelve-lead electrocardiogram of the index patient at 1-year follow-up. Twelve-lead electrocardiogram obtained 1 year after initiation of β -blocker therapy and implantation of a subcutaneous implantable cardioverter-defibrillator (S-ICD), demonstrating sinus rhythm at 60 beats per minute, normal frontal QRS axis, normal PR interval, narrow QRS complexes without pathologic Q waves, and broad T waves with subtle terminal notching in lead V2. The blue bracket in lead aVL indicates the measured QT interval, corresponding to a Bazett-corrected QTc of 500 ms. At this time point, the index patient was asymptomatic, and no appropriate or inappropriate S-ICD therapies or device-related complications had been recorded.

LQTS2 (**Figure 4**). Standardized exercise testing and the standing test (Viskin test) showed no diagnostic QTc abnormality, and she was referred for catheter ablation because symptomatic ventricular ectopy persisted despite medical therapy. At 1-year follow-up, the index patient remained asymptomatic while receiving propranolol 1 mg/kg twice daily, with persistent QTc prolongation and no appropriate or inappropriate S-ICD therapies or device-related complications (**Figure 5**). The chronology of clinical events, diagnostic evaluation, and management is summarized in **Supplementary Figure 1**.

Discussion

We describe a pediatric case initially misdiagnosed as epilepsy in which the surface electrocardiogram ultimately revealed an underlying cardiac channelopathy. Although many individuals with congenital LQTS remain asymptomatic for prolonged periods, delayed recognition may result in life-threatening arrhythmic presentations, including syncope, seizure-like episodes, or sudden cardiac arrest.⁽⁹⁾

Lead II or V5 optimally balances feasibility and risk stratification for QT measurement; V2–V3 often yield longer QTc values yet are less predictive.⁽¹⁾ A QTc ≥ 450 ms in men or ≥ 460 ms in women increases the likelihood of congenital LQTS. However, values within this range may still be encountered in up to 10% of the general population.^(2,3)

Under contemporary consensus standards, a clinical diagnosis of LQTS is supported by a QTc ≥ 480 ms or a Schwartz score >3 ; when arrhythmic syncope or resuscitated cardiac arrest has been documented, a QTc ≥ 460 ms is considered sufficient for diagnosis.⁽⁴⁾ Genotype-positive relatives, even with normal QTc values, remain at measurable risk for ventricular arrhythmias. Up to 15% of clinically definite cases remain genotype-negative, highlighting the limited sensitivity of current gene panels and the resulting challenges for diagnostic certainty.^(2,4)

LQTS type 2 accounts for approximately 25%–30% of congenital LQTS and is characterized by a clinical penetrance of roughly 75%–80%. Cardiac events occur in nearly half of affected individuals, with sudden cardiac death in 4%, and annual mortality approaching 0.5%.^(1,2) The resting electrocardiogram typically demonstrates low-amplitude T waves with terminal notching or bifid morphology, although this pattern is absent in over 20% of genotype-positive individuals due to incomplete penetrance.^(3,10) LQTS type 2 due to a pathogenic KCNH2 variant was confirmed by genetic testing in our patient. KCNH2 encodes the Kv11.1 α -subunit, which conducts the rapidly activating delayed-rectifier potassium current (IKr). Loss of IKr delays phase 3 repolarization, prolonging action-potential duration and thereby establishing an electrophysiological substrate for early afterdepolarizations and triggered ventricular arrhythmias, culminating in TdP.⁽¹¹⁾ In a 201-patient cohort, pore-region variants were linked to higher rates of cardiac events than non-pore-region variants.⁽¹²⁾ This patient's pore-region KCNH2 variant therefore denotes a markedly heightened vulnerability to malignant ventricular arrhythmias and sudden cardiac death.

An electrocardiogram should be considered after a first afebrile generalized seizure, particularly when clinical features are atypical or when the electroencephalogram is normal. Phenotypic overlap is well established, particularly in long-QT syndrome type 2, in which KCNH2 expression in both myocardial and hippocampal tissue has been proposed as a potential substrate for epileptiform manifestations.⁽¹³⁾ This case highlights the importance of early electrocardiographic evaluation after an atypical first seizure. Therapeutic management of LQTS begins with universal trigger avoidance and β -blockade, with nonselective agents such as nadolol or propranolol generally favored.^(4,14) In addition to β -blockade, implantable cardioverter-defibrillator (ICD) implantation is recommended after an index cardiac arrest and in patients with persistent symptoms despite optimized β -blocker therapy or when β -blockers are not tolerated or are contraindicated. ICD implantation may also be considered in asymptomatic

individuals judged to be at very high risk based on integrated clinical and genetic risk stratification tools, including the 1–2–3 LQTS calculator.^(15,16) In this case, persistent QTc prolongation despite β -blocker therapy, a pathogenic KCNH2 substrate yielding a 9.3% predicted risk (>5%) on the 1–2–3 LQTS calculator, and suspected prior unrecognized cardiac arrest collectively justified subcutaneous ICD implantation.

ICD therapy is not universal in congenital LQTS; expert centers report device implantation in only 3%–10% of patients. S-ICDs avoid intravascular leads and the substantial long-term failure and extraction risks associated with transvenous systems.⁽¹⁷⁾ In inherited channelopathies, the EFFORTLESS registry has shown S-ICD performance comparable to transvenous systems, with similar overall complication and appropriate shock rates and a trend toward fewer inappropriate shocks.⁽¹⁸⁾ Collectively, these data favor restrained, risk-stratified implantation and justify S-ICD selection in young genotype-positive patients. Among exercise-derived parameters, the QTc measured at 4-minute recovery has shown the greatest discriminatory value in some series; a recovery QTc ≥ 445 ms has been reported to yield high sensitivity and specificity for LQTS, and in borderline cases, a QTc increase >50 ms at peak heart rate may further support the diagnosis.⁽¹⁹⁾ Orthostatic testing is lower-yield and adjunctive. In the proband's sister, standardized exercise

testing and a standing test (Viskin test) showed no diagnostic QTc abnormality, lowering the likelihood of congenital LQTS.^(3,20) Cardiac genetic testing then confirmed the absence of the familial KCNH2 variant, averting misclassification and device therapy and directing catheter ablation of an idiopathic right ventricular outflow tract focus. The principal limitation of this report is incomplete cascade screening of first-degree relatives, reflecting constrained local access to comprehensive genetic diagnostics. In conclusion, pediatric seizure-like episodes, particularly when the electroencephalogram is normal, should prompt immediate electrocardiography to exclude long-QT syndrome; in this case, KCNH2 genotyping confirmed the diagnosis and refined risk stratification.

Ethical Considerations

This case report received approval from the institutional ethics committee. Written informed consent authorizing publication of the clinical information and accompanying materials was obtained from the patient's mother.

Author's Contribution

AVB, ACA, RCG, CRG: Conceptualization, research, drafting of the original manuscript, revision and editing of the manuscript.

RSB, MCS, CGC, AGL, ACP, MPR, PZC: supervision, review, and editing.

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