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Family long QT syndrome type 2 associated with *KCNH2* gene mutation: aborted sudden cardiac death

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Abstract

A complete screening was performed in a family after one of its members presented with a sudden cardiac death event. A genetic analysis revealed a mutation that led to a long QT syndrome.

Introduction

A clinical evaluation of a family was carried out after an aborted sudden cardiac death event in one of the members (proband), studying the possible causes. Long QT syndrome (LQTS) type 2 associated with a mutation of the *KCNH2* gene with the pathogenic heterozygous variant C.2775dup (p.pro926ALAFS*14) was found in the proband, so the rest of the family was screened for this disease. All case characteristics are summarized in Table 1.

Case Report #1

A 44-year-old female with a 25-year history of epilepsy presented a high-risk syncope during a bicycle ride, which led to multiple face injuries. She was hospitalized for facial reconstruction, and during post-operative care, she presented with a sudden cardiac death episode due to ventricular tachycardia, which was aborted with electric cardioversion (Figure 1). The resting 12-lead electrocardiogram (ECG) showed a QTc interval of 520 ms and notched T wave in 3 leads. A 24-hour Holter monitoring was performed, which reported an average QTc interval of 538 ms and a maximum corrected QT (QTc) interval of 775 ms. The patient did not consume any medication that could explain the long QT. A genetic analysis was performed. The c.2775dup (p.Pro926Alafs*14) mutation was confirmed, one of many mutations for *KCNH2*. The patient received pharmacological treatment with propanolol, and as part of secondary prevention of sudden cardiac death, placement of an implantable cardioverter-defibrillator was performed. In early follow-up, she did not present discharges. Once the genetic diagnosis of LQTS of the proband was made, her offspring were screened for this condition.

Case Report #2

A 25-year-old male (son), a high-performance athlete, with no previous medical history, was found cardiovascularly asymptomatic. On a 12-lead resting ECG, the patient presented a QTc of 568 ms and a notched T wave in 3 leads. A 24-hour Holter monitoring was performed, which reported an average QTc interval of 500 ms and a maximum QTc interval of 648 ms. We performed a Viskin test, which was positive, with a basal QTc interval of 568 ms, a resting

phase QTc of 525 ms, and a standing QTc in the first minute of 614 ms (Figures 2 and 3). A transthoracic echocardiogram was conducted without evidence of structural heart disease. A Schwartz Index score of 5 points was assessed, with a high probability of having LQTS. Genetic analysis showed the same mutation as the proband. The patient received pharmacological treatment with nadolol 40 mg daily and was not considered a candidate for a defibrillator.

Case Report #3

A 28-year-old female (daughter), with no previous medical history, was found cardiovascularly asymptomatic. On a 12-lead resting ECG, the patient presented a QTc of 447. A 24-hour Holter monitoring reported an average QTc interval of 435 ms and a maximum of 471 ms. The transthoracic echocardiogram did not reveal evidence of structural heart disease. A Schwartz Index score of 3 points was assessed. She did not present any mutation in the genetic analysis. Periodic follow-up with ECG will be performed.

Discussion

LQTS is an inherited cardiac channelopathy characterized by QT prolongation and T-wave abnormalities on the ECG, which can be fatal. There are too many specific mutations that can produce this

Table 1. Case characteristics and studies performed.

	Case #1	Case #2	Case #3
History	44-year-old woman with a history of epilepsy	25-year-old man, high-performance athlete	28-year-old woman
Clinical presentation	High risk syncope and sudden cardiac death (ventricular tachycardia)	Asymptomatic	Asymptomatic
ECG	QTc: 520 ms. T-wave notching in 3 leads	QTc: 568 ms. T-wave notching in 3 leads	QTc 447 ms
Schwartz score	6	5	3
24-hour Holter monitor	Average QTc 538 ms Max QTc: 775 ms	Average QTc 500 ms Max QTc: 648 ms	Average QTc 435 ms Max QTc 471 ms
Viskin test	Negative	Positive	Negative
Mutationc.2775dup	Positive	Positive	Negative

ECG, electrocardiogram; QTc, corrected QT.

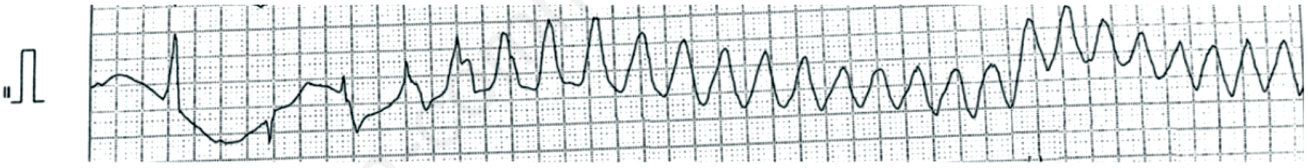

Figure 1. DII lead. Cardiac sudden death event due to ventricular tachycardia.

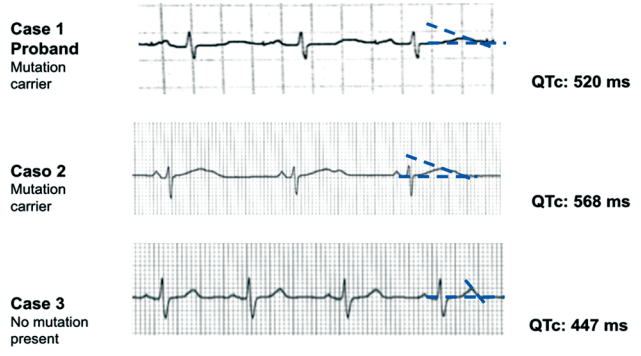

Figure 2. Cases baseline corrected QT interval using Bazett formula. Cases #1 and #2 presented with long QT syndrome.

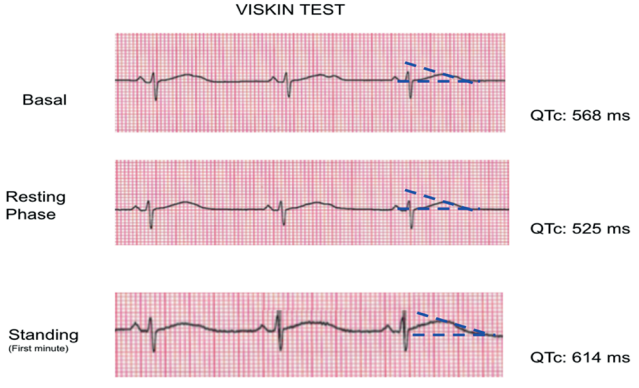

Figure 3. The Viskin Test performed on case 2 was positive, with a basal corrected QT (QTc) interval of 568 ms, a resting phase QTc of 525 ms, and a standing QTc in the first minute of 614 ms.

condition, but approximately 75-90% of LQTS are caused by three susceptible genes [1,2].

The three most common LQTS types are LQTS1, associated with mutations in the *KCNQ1* gene, producing a loss-of-function in slowly activating potassium channel Kv7.1; LQTS2, caused by a loss-of-function mutation in *KCNH2* (hERG); and LQTS3, caused by mutations in *SCN5A*, resulting in an increased INa current [3].

The pathogenesis of LQTS present in the cases is explained because of the decreased functionality in the hERG channel, which is a voltage-gated K+ channel involved in the IKr current, resulting in a decreased K+ efflux in phase III of the cardiac action potential [1]. The result is that the influx Ca2+ current (phase II) is greater than the efflux of phase III, causing a lack of repolarization and a prolonged depolarization, which can cause an early afterdepolarization [3]. The QT interval shows the time from the beginning of ventricular depolarization to the complete repolarization; the result of this mutation is a prolongation of this interval because the K+ efflux is not enough to repolarize all the ventricular cells (particularly Purkinje fibers and M cells). With a longer action potential duration, a more refractoriness zone is caused, and as a result, an increased probability of reentry arrhythmias is present [1]. Torsades de pointes (TdP) is the main reentry arrhythmia and the hallmark of fatal LQTS [3]. TdP can explain all the symptoms from syncope (if it is transient) to ventricular fibrillation and sudden cardiac death if it is prolonged [4,5].

All LQTS types have the same clinical presentation spectrum: they can be asymptomatic or present with symptoms such as palpitations, syncope, dizziness, seizures, or even sudden cardiac death, which can be the first manifestation in a carrier family [3,6].

Diagnosis is based on clinical manifestations, ECG features, family history, and genotype tests. The hallmark is the prolongation of the QT interval on a 12-lead ECG. The diagnosis is made by a QTc>460 ms in women and QTc>450 ms in men [3].

The last update for Schwartz score was published in 2011, with the addition of a QTc at the 4th minute of recovery from the exercise stress test ≥480 ms; and the most recent cut-off point is set to 3.5 points to identify a high probability of LQTS [3,7,8]. Although this score may underestimate some patients and may not help silent mutation carriers, it becomes useful for the selection of patients who should be tested for genotype screening when there is a score of 3.0 or more [2].

Genetic testing is based on clinical suspicion and family history because approximately 4-8% of all people have variants of uncertain significance in the three major genes. When there is a high suspicion, it is recommended to test the index case, and if LQTS is confirmed, mutation-specific gene tests must be done in all first-degree relatives [3,5,8].

The Viskin test is a simple maneuver based on the response of the QT interval to the heart rate provoked by standing [3]. The QT interval is expected to shorten as the heart rate increases in response to standing, but in patients with LQTS, the QT interval increases after standing [9].

The current management is based on three medical therapies: β-adrenergic blocking agents (βB) are the first-line therapy in patients with LQTS. The two βB preferred are nadolol and propranolol [1,2,10]. Despite the widespread use of propranolol, nadolol significantly lowers arrhythmic risk across all genotypes due to its pharmacokinetic properties, allowing for a single daily administration [3].

The other two medical therapies are left cardiac sympathetic denervation (LCSD) and implantable cardioverter defibrillators (ICD) [1,10]. ICD is not indicated in all patients; it is recommended as primary prevention in patients who remain symptomatic (presenting with syncope or ventricular arrhythmias) despite β-blocker and genotype-specific therapies or in cases where medical therapy is not tolerated at the therapeutic dose. ICD is recommended as secondary prevention in addition to β-blockers in patients with a previous episode of cardiac arrest [10]. LCSD is now a rarely performed procedure. It consists of a high thoracic left sympathectomy of the lower half of the stellate ganglion, and it is an option for patients with high-risk LQTS for whom βB therapy is not effective, and ICD is contraindicated [5,10].

Conclusions

The present case series highlights the importance of deepening the complete study of patients with sudden cardiac death, including genetic analysis, since it is essential to specify the risk, type of treatment, and prognosis for the rest of the family members.

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