ORIGINAL ARTICLE

Genetic and Clinical Characteristics of Patients with Congenital Long QT Syndrome- Genotype. Experiences During Long-Term Follow-Up

Características genéticas y clínicas de los pacientes con genotipo asociado al síndrome QT largo congénito. Experiencias durante un seguimiento a largo plazo

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ABSTRACT

Background: Congenital long QT syndrome (LQTS) is an inherited channelopathy with a broad genetic spectrum but with a common phenotypic manifestation, the prolonged QT interval. However, its clinical presentation and natural history are highly variable.
Objectives: The aim of this study was to define the genetic and clinical characteristics of patients with congenital LQTS during a long-term follow-up.
Methods: Retrospective cohort study of patients with congenital LQTS genotype. The incidence of serious events at follow-up was defined. Quantitative variables are expressed as median and interquartile range (IQR) and qualitative variables as frequency and percentage.
Results: Forty-four patients were included. Thirty percent of patients had LQTS1 genotype, 65% LQTS2 genotype and 5% LQTS3 genotype; 57% of cases carried the missense mutation, 11% the nonsense mutation and 32% the frameshift mutation. The corrected QT interval was 490 msec (IQR 462-498). The phenotype was present in 66% of patients, but it remained permanently only in 32%. Syncopal episodes occurred in 39% of patients. Cardiac arrest was the first manifestation in 7% of cases. Syncope recurred in 11% of patients even after pharmacological therapy, and 5% suffered sudden death. Seven patients received an implantable cardiodefibrillator (ICD). Among them, 29% received shocks due to ventricular tachycardia or ventricular fibrillation (VT/VF) and 58% presented device-related complications.
Conclusions: Most patients had the LQTS1 or LQTS2 genotype, the intermittent phenotype, and a good response to treatment. Implantation at an early age and the high rate of complications during long-term follow-up require careful evaluation when indicating an ICD.

Key words: Long QT syndrome - Sudden death - Syncope - Genetic mutation - Implantable cardiodefibrillators

RESUMEN

Introducción: El síndrome de intervalo QT largo (SQTL) congénito es una canalopatía hereditaria con un gran espectro genético pero una manifestación fenotípica en común, el intervalo QT prolongado. Sin embargo, la presentación clínica y la historia natural es muy variable.
Objetivos: Definir el perfil de las características genéticas y clínicas de los pacientes con SQTL congénito durante un seguimiento a largo plazo.
Material y métodos: Estudio de cohorte retrospectiva de pacientes con genotipo de SQTL congénito. Se definió la incidencia de eventos serios en el seguimiento. Las variables cuantitativas se expresan como mediana y rango intercuartilo (RIC) y las cualitativas como frecuencia y porcentaje.
Resultados: Fueron incluidos 44 pacientes. El 30% tenía el genotipo de SQTL1, el 65% el de SQTL2 y 5% el de SQTL3. El 57% tenía la mutación *missense*, el 11% *nonsense* y el 32% *frameshift*. El intervalo QT corregido fue de 490 mseg (RIC 462-498). El 66% manifestó el fenotipo, pero solo el 32% de manera permanente. El 39% tuvo episodios sincopales. El paro cardíaco fue la primera manifestación en el 7%. El 11% tuvo recurrencia de síncope aún luego de terapia farmacológica y el 5% padeció muerte súbita. Siete pacientes recibieron un cardiodesfibrilador implantable (CDI). De ellos, el 29% tuvo choques por taquicardia o fibrilación ventricular (TV/FV) y el 58% complicaciones asociadas a los dispositivos.
Conclusiones: La mayoría de los pacientes tenían el genotipo de SQTL1 o SQTL2, el fenotipo intermitente y una buena respuesta

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al tratamiento. La edad temprana del implante y la elevada tasa de complicaciones asociadas al largo plazo exigen una evaluación personalizada al momento de indicar el CDI.

Palabras claves: Síndrome QT largo - Muerte súbita – Síncope - Mutación genética - Cardiodesfibrilador implantable

INTRODUCTION

Congenital long QT syndrome (LQTS) is characterized by prolongation of the ventricular myocardial action potential due to increased sodium and calcium inward currents (INa and ICaL) or decreased potassium outward currents (IKs, IKr and IK1). So far, mutations in 20 different genes encoding cardiac ion channels and/or modulatory proteins directly or indirectly involved in the genesis of these currents have been identified. (1)

With a prevalence in the general population of 1 in 2000 individuals, it is no longer an exceptional situation to see a patient with a prolonged QT interval in daily medical consultation for sports, schooling or pre-employment. (2)

With the advance of computer technology and genetic engineering, hundreds of variants have been identified in each of the genes involved in LQTS that, through different types of mutations, alter the function of myocyte ion channels. Most mutations show an autosomal dominant inheritance pattern. Thus, individuals are born with the mutation causing the disease and live with it throughout their lives.

All affected individuals have a common phenotypic manifestation, the prolongation of ventricular repolarization duration. However, the existence of a broad clinical variability among patients raises questions about the epigenetic factors that modulate their phenotypic expression. Even when patients are born with the pathogenic genotype, the phenotype may never manifest itself, become evident late or, in some cases, only do so intermittently, expressing itself only on certain days, and remaining totally asymptomatic for prolonged periods of time. Similarly, the risk of suffering adverse cardiac events may vary among carriers of the same genetic variant and even in the same person, depending on the situation to which he/she has been exposed. (3)

In this study, we have evaluated the clinical and genetic characteristics of patients diagnosed with LQTS by means of a genetic study with massive parallel sequencing and long-term clinical follow-up for more than 10 years, thus allowing the assessment of both the natural history of the disease and the occurrence of adverse cardiac events (syncope, ventricular tachyarrhythmia and/or sudden cardiac death), the response to pharmacological treatment and/or implantable antiarrhythmic devices, and their associated complications.

METHODS

A retrospective study was designed selecting individuals with suspected congenital LQTS attending Hospital General de Ramos Mejía. The following inclusion criteria were used: men and women aged 5 to 70 years; clinical suspicion of congenital LQTS (QTc interval ≥480 milliseconds on the ECG or Schwartz score ≥3); and identification of a pathogenic variant of congenital LQTS in a genetic study. Those with any of the following criteria were excluded: LQTS acquired by medication; refusal to sign the informed consent; patients under 18 years of age, without parental or legal guardian consent; and negative genetic study. Simultaneous 12-lead ECG recordings were obtained from each patient. QT intervals were corrected for heart rate (QTc) using Bazett's formula ($QTc = QT/\sqrt{RR}$, in seconds).

For sequence analysis and deletion/duplication testing, massive parallel sequencing (NGS) was used with a panel of more than 150 genes for arrhythmias and cardiomyopathies (ABCC9, ACADVL, ACTC1, ACTN2, AGL, ALMS1, ALPK3, BAG3, BRAF, CACNA1C, CACNA1D, CALM1, CALM2, CALM3, CASQ2, CBL, CDH2, CPT2, CRYAB, CSRP3, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, ELAC2, EMD, EYA4, FHL1, FKRP, FKTN, FLNC, GAA, GATA4, GATA5, GJA5, GLA, HCN4, HRAS, JUP, KCNE1, KCNH2, KCNJ2, KCNQ1, KRAS, LAMP2, LMNA, LZTR1, MAP2K1, MAP2K2, MRAS, MTO1, MYBPC3, MYH7, MYL2, MYL3, MYL4, MYLK3, NF1, NKX2-5, NRAS, PCCA, PCCB, PKP2, PLN, PPA2, PPCS, PPP1CB, PRKAG2, PTPN11, RAF1, RASA1, RBM20, RIT1, RYR2, SCN5A, SDHA, SGCD, SHOC2, SLC22A5, SOS1, SOS2, SPRED1, TAZ, TBX20, TCAP, TMEM43, TMEM70, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TRDN, TRPM4, TTN, TTR, VCL, A2ML1, AKAP9, ANK2, ANKRD1, CACNA2D1, CACNB2, CALR3, CAV3, CHRM2, CTF1, CTNNA3, DTNA, FHL2, GATA6, GATAD1, GPD1L, HAND1, ILK, JPH2, KCNA5, KCND3, KCNE2, KCNE3, KCNE5, KCNJ5, KCNJ8, KCNK3, KIF20A, KLF10, LAMA4, LDB3, LRRC10, MAP3K8, MED12, MYH6, MYLK2, MYOM1, MYOZ2, MYPN, NEBL, NEXN, NPPA, PDLIM3, PLEKHM2, PRDM16, RANGRF, RASA2, RRAS, SCN10A, SCN1B, SCN2B, SCN3B, SCN4B, SLMAP, SNTA1, TMPO, TXNRD2), developed by Invitae® (1400 16th Street, San Francisco, CA 94103, USA). USA). Genomic DNA obtained from a peripheral blood sample was enriched for target regions using a hybridization-based protocol and sequenced using Illumina® technology. All target regions were sequenced to a depth ≥50× or supplemented with additional analyses. Readings were aligned to a reference sequence (GRCh37) and sequence changes were identified and interpreted in the context of a single clinically relevant transcript. Enrichment and analysis were focused on the coding sequence of the indicated transcripts, 20 base pairs (bp) of flanking intronic sequence, and other specific genomic regions shown to be disease-causing at the time of assay design. Detected variants were evaluated by probing the following databases: dbSNP from NCBI (National Center for Biotechnology Information, https://www.ncbi.nlm.nih.gov/snp/), ExAC (Exome Aggregation Consortium, https://exac.broadinstitute.org), gnomAD (Genome Aggregation Database, https://gnomad.broadinstitute.org/) and OMIM (Online Mendelian Inheritance in Man, https://omim.org/).

The pathogenicity of variants was estimated using three different types of prediction software: SIFT (https://sift.bii.a-star.edu.sg/), PolyPhen-2 (https://genetics.bwh.harvard.edu/pph2/) and Align-GVGD (https://bio.tools/align-gvgd/).

Variants were classified as pathogenic or probably pathogenic, of uncertain significance, and probably benign or benign using an evidence scoring system based on the consensus of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. (4) Results were classified as positive, negative, carriers or uncertain, according to the classification of the identified variant and the inheritance pattern of the associated condition.

Statistical analysis

Quantitative variables are expressed as median and interquartile range (IQR) and qualitative variables as frequency and percentage.

Ethical considerations

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Hospital General de Agudos Dr. José María Ramos Mejía, Autonomous City of Buenos Aires, Argentina.

RESULTS

Forty-four patients with a genetic diagnosis of LQTS were followed-up for 46 months (IQR35-175). Among them, 26 (59%) were women, and median age was 30 years (IQR 20-49). Thirty-five patients (80%) reported a history of sudden cardiac death (SCD) in first- and second-degree relatives.

From the total number of patients, 13 (30%) corresponded to the LQTS type 1 genotype (KCNQ1 gene), 29 (65%) to LQTS type 2 (KCNH2 gene) and 2 (5%) to LQTS type 3 (SCN5A gene). The missense point mutation was identified in 25 patients (57%), five patients (11%) carried a nonsense mutation and a frameshift mutation was found in 14 patients (32%). The corrected QT interval was 490 msec (IQR 462-498). The phenotypic manifestation of LQTS (QTc >480 msec) was observed in 29 patients (66%). However, only 14 individuals (32%) manifested a permanent phenotype (Table 1).

Syncopal episodes were observed in 17 individuals (39%), especially during adolescence. Cardiac arrest was the first clinical manifestation in 3 patients (7%). The age at which symptoms began to be manifest was 17 years (IQR 14-25).

Ninety-three percent of cases were treated with beta-blockers (72% with propranolol), and 2 patients (5%) with a diagnosis of LQTS type 3 were treated with a sodium channel blocker (flecainide). Five patients (11%) had recurrence of syncope even after drug therapy. Two individuals with LQTS type 2 (5%) suffered nocturnal SCD at 17 and 66 years of age.

On the other hand, 7 patients required implantable cardiodefibrillator (ICD) at 18 years of age (IQR 16-26). Of these, 29% received shocks due to tachycardia or ventricular fibrillation (VT/VF) and 58% had complications associated with implantable devices (infection or catheter displacement/fracture) during the 161 month (IQR 83-229) follow-up (Table 2).

DISCUSSION

Congenital LQTS described by Jervell and Lange-Nielsen in 1957 and Romano and Ward in 1964 is an inherited channelopathy characterized by an alteration in ventricular repolarization and manifested by an abnormal prolongation in QTc interval duration. It predisposes to the onset of potentially lethal ventricular tachyarrhythmias (torsade de pointes and/

Table 1. Genetic and clinical characteristics (n=44)

Variable		
KCNQ1 (SQTL1)	13	30%
KCNH2 (SQTL2)	29	65%
SCN5A (SQTL3)	2	5%
Nonsense	5	11%
Missense	25	57%
Frameshift	14	32%
Relative with SCD	35	80%
Syncope	17	39%
Cardiac arrest	3	7%
QTc (msec)	490 (IQR 462-498)	
QTc ≥480 msec.	29	66%
Permanent phenotype	14	32%

SCD: sudden cardiac death.
Qualitative variables are presented as frequency and percentage, and quantitative variables as median and interquartile range (IQR)

Table 2. Treatment and adverse cardiac events during follow-up. (n=44)

Follow-up		
Beta-blockers	41	93%
Sodium channel blockers	2	5%
Recurrence of syncope	5	11%
SCD	2	5%
ICD Implant	7	16%
Implant age	18 (IQR 16-26)	
ICD replacement (number of devices/patient)	2.1	
ICD shock due to VT/VF	2	29%
ICD-associated infection	2	29%
Displacement or fracture of catheter	2	29%

ICD: implantable cardiodefibrillator; SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia.

Qualitative variables are presented as frequency and percentage and quantitative variables as median and interquartile range (IQR). Percentages of shock, infection and catheter displacement refer to the 7 patients who received ICDs.

or ventricular fibrillation) that usually occur due to increased adrenergic tone following auditory stimuli, physical exercise or emotional stress. (5,6)

Over the past 25 years, 20 genes have been associated with congenital LQTS. However, a recent analysis reclassified several of these genes as having limited or controversial evidence. (7) This approach has left seven genes with definite or strong evidence of causality (KCNQ1, KCNH2, SCN5A, CALM1, CALM2, CALM3, and TRDN). All these genes encode ion channels involved in cardiac repolarization or proteins that regulate or modulate ion channel function.

Ninety percent of individuals with LQTS genotype carry mutations in one of the 3 major disease genes: KCNQ1 (LQTS type 1), KCNH2 (LQTS type 2), and SCN5A (LQTS type 3), which encode the alpha subunits of the Kv7.1 (IKs), Kv11.1 (IKr), and Nav1.5 (INa) ion channels, respectively (Figure 1). (8,9)

Approximately 40% of mutations correspond to nonsense mutations (consisting of a point mutation in the DNA sequence resulting in a premature termination codon), or frameshift mutations caused by the insertion or deletion of nucleotides in a DNA sequence, which generates a reading frame completely different from the original. These mutations alter protein synthesis and generate defective alpha subunits of ion channels. The remaining 60% are missense mutations, where a single nucleotide change alters an amino acid codon (Figure 2). These mutations can alter pore permeability, activation/deactivation or intracellular trafficking of ion channels. (10)

In our study, patients showed a genetic profile similar to the aforementioned studies. Ninety-five percent of the patients were carriers of the LQTS type 1 (KCNQ1) or LQTS type 2 (KCNH2) genotypes. The predominant genetic variants were due to missense point mutations with a single amino acid change in the protein sequence

Frequently, the intermittent nature of the LQTS phenotype manifestation hinders patient diagnosis. In our study, most patients (66%) manifested the LQTS phenotype (QTc >480 msec) but only one third had the permanent phenotype. These results were comparable to those of the study by Yoo et al. in which patients with LQTS showed significant QT interval oscillations in different measurements and only 20%

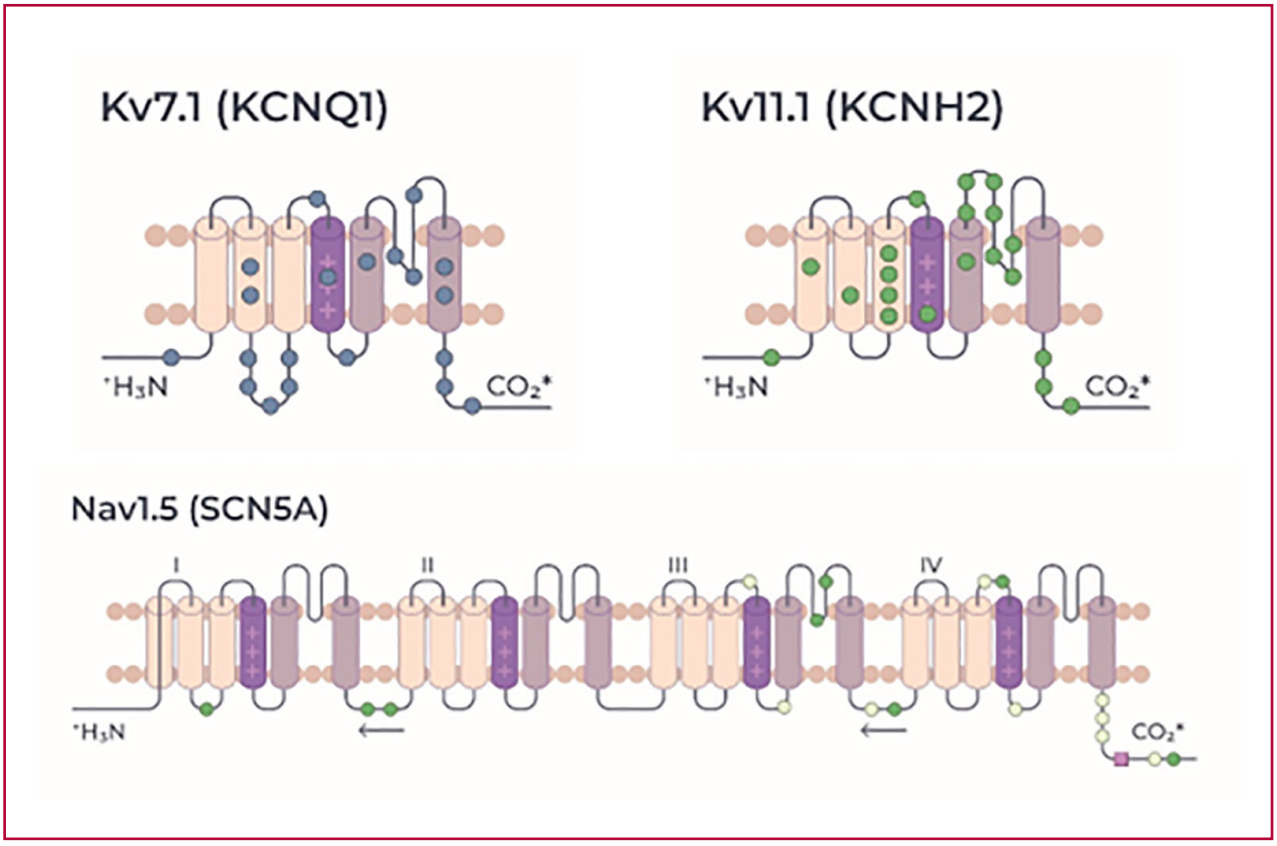
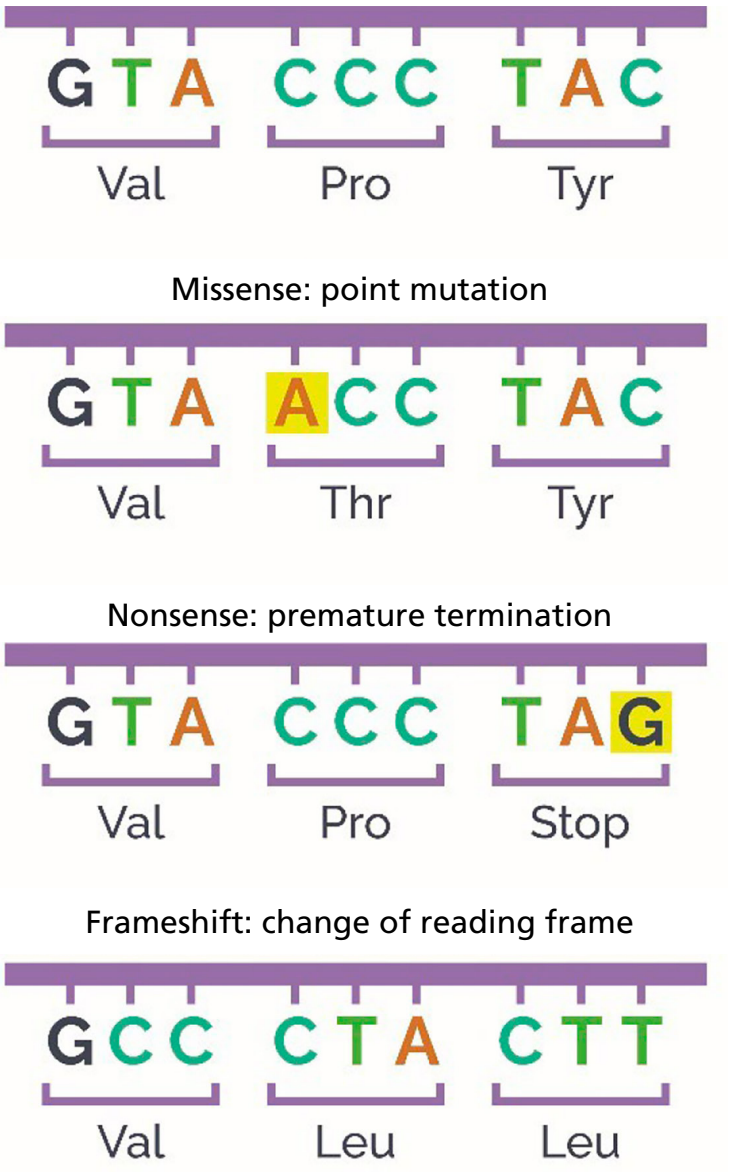


Fig. 1. Ion channels involved in LQTS type 1, type 2 and type 3. The KCNQ1 gene encodes the alpha subunit of the voltage-dependent potassium channel Kv7.1 (responsible for the slow delayed rectifier current, IKs) and the KCNH2 gene encodes the alpha subunit of the voltage-dependent potassium channel Kv11.1 (responsible for the rapid delayed rectifier current, IKr). The voltage-dependent sodium channel Nav1.5 (responsible for INa current) is encoded by the SCN5A gene. Modified from: Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. Physiol Rev 2005;85:1205-53. https://10.1152/physrev.00002.2005



DNA sequence: A: adenine; T: thymine; C: cytosine; G: guanine. Amino acid sequence: Ser: serine; Val: valine; Pro: proline; Tyr: tyrosine; Thr: threonine; Leu: leucine; Stop: premature termination codon.

Fig. 2. Types of mutations. Missense: DNA point mutation that changes an amino acid. Nonsense: DNA point mutation that introduces a premature termination codon. Frameshift: insertion or deletion of DNA with a change of the reading frame. Modified from: Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. Physiol Rev 2005;85:1205-53. https://10.1152/physrev.00002.2005

maintained the permanent phenotype. (11) These findings suggest that to achieve the diagnosis of congenital LQTS, patients should be thoroughly and continuously evaluated by serial ECG, stress ECG or dynamic recording with Holter monitoring on a periodic basis. In these circumstances, genetic testing to identify the responsible pathogenic variant becomes crucial for the early and accurate detection of patients with congenital LQTS.

Individuals with LQTS often manifest the phenotype and suffer syncopal episodes and/or sudden death at an early age. Mortality in patients with LQTS ranges from 1% to 2% at 5 years. (12) Beta-blockers are effective, especially in LQTS1 in which VT/VF is triggered by exertion. Non-compliance with treatment and the use of drugs that prolong the QT interval are mainly responsible for therapeutic failures. (13,14) In LQTS2 and LQTS3, lethal arrhythmic events are usually triggered at rest or by auditory or emotional stimuli. (15,16) Among individuals with ICD, the rate of recurrent events is approximately 3% to 28% within 5 years. (17,18)

There is still a tendency to consider it unnecessary to identify the genotype of patients with LQTS, once

the diagnosis has been made using clinical criteria. This conduct makes it impossible to initiate cascade screening of the affected family. Considering that the response to drugs (beta-blockers vs. sodium channel blockers) and the stimuli that act as arrhythmogenic triggers (exercise, auditory or emotional) are very different between genotypes, the lack of knowledge of the genetic cause makes it difficult to provide adequate therapy to patients. The consequences could result in avoidable deaths, especially among genotype-positive and phenotype-negative individuals. Thus, molecular biology should no longer be considered as an exclusive field of research but as an essential, everyday medical tool. (19)

In our study, ICD implantation was indicated between the second and third decade of life. The main reason was the occurrence of recurrent syncope even with beta-blocker therapy (primary prevention). The 2 women (one with LQTS1 and the other with LQTS2) who received an ICD for secondary prevention had adequate therapy for VT/VF 2 to 6 years after implantation. On the other hand, the rate of device-associated complications (infection or catheter displacement/fracture during long-term follow-up) was high. According to current guidelines, ICD implantation is indicated for secondary prevention (in individuals who have suffered resuscitated cardiac arrest, class I) and primary prevention (in those with recurrent syncope under beta-blocker treatment, class IIa). (20) Clearly, the decision to implant an ICD is life-saving in patients at high risk of SCD. However, in congenital LQTS, as in other hereditary channelopathies, the very early age of diagnosis and device implantation and the high rate (more than 20% in 5 to 10 years) of associated complications (infection, myocardial perforation, displacement, catheter wear and/or fracture, psychological consequences, etc.) that occur throughout the life of the patients, suggest that the decision to indicate an ICD should be based on a thorough and cautious evaluation. (21,22)

CONCLUSIONS

The genetic profile of our patients coincides with that reported in the literature. The identification of the genotype allows us to screen for asymptomatic carriers who do not express the phenotype permanently, thus achieving an accurate diagnosis and early treatment through the cascade screening strategy of relatives. Most patients respond favorably to beta-blockers. However, there is a high-risk group (previous VT/VF) that requires ICD implantation to prevent SCD. The early age of implantation and the high rate of associated long-term complications require a personalized and thorough evaluation at the time of implantation.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web).

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Características genéticas y clínicas de los pacientes con genotipo asociado al síndrome QT largo congénito. Experiencias durante un seguimiento a largo plazo
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