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705

Original Article

Left Cardiac Sympathetic Denervation in Long QT Syndrome: Analysis of Therapeutic Nonresponders

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Background—Left Cardiac Sympathetic Denervation (LCSD) has become an important additional option in the prevention of sudden cardiac death in Long QT Syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia. However, left cardiac sympathetic denervation (LCSD) has become an important additional option in the prevention of sudden cardiac death in LQTS and catecholaminergic polymorphic ventricular tachycardia. Thought to be because of the attenuation of localized neural/sympathetic chain release of norepinephrine and an increased ventricular fibrillation threshold, LCSD’s antifibrillatory effects in LQTS are well documented with an estimated 90% reduction of cardiac events postdenervation surgery overall.1,6

Methods and Results—We performed retrospective chart review for 52 consecutive patients (24 males; mean age at diagnosis, 10.0±10 years; mean QTc, 528±74 ms) with LQTS who underwent LCSD between 2005 and 2010 (mean age at LCSD, 14.1±10 years) and have been followed up for 3.6±1.3 years. A BCE was defined as either (1) an appropriate ventricular fibrillation-terminating implantable cardioverter defibrillator shock or (2) arrhythmogenic syncope, seizures, or aborted cardiac arrest after LCSD. Thirty-three patients (61%) had LCSD as primary prevention because of either high-risk assessment or β-blocker intolerance. So far, 12 of 52 (23%) patients (7 males) have experienced ≥1 BCE post LCSD. The clinical phenotype of patients with BCEs was significantly more severe than patients without a BCE. No BCEs were seen in patients undergoing LCSD for β-blocker intolerance (0/12 versus 17/40; P<0.001).

Conclusions—Although a marked reduction in number of cardiac events is usually seen after LCSD, ≥50% of high-risk LQTS patients have experienced ≥1 post-LCSD breakthrough. Therefore, LCSD must not be viewed as curative or as an alternative in implantable cardioverter defibrillator for high-risk patients. Prophylactic LCSD may provide another option to counter a suboptimal quality of life resulting from medication-related side effects. (Circ Arrhythm Electrophysiol. 2013;6:705-711.)

Key Words: arrhythmias, cardiac death sudden, cardiac left cardiac sympathetic denervation long QT syndrome syncope

Clinical Perspective on p 711

Herein, we present our experiences with the first 52 LQTS patients referred for LCSD therapy at our institution with particular focus on those patients experiencing ≥1 breakthrough cardiac event (BCE) post denervation. The phenotype of those patients who did not respond to LCSD therapy (ie, the nonresponders) and the option of using LCSD for patients who are intolerant to β-blockers were examined closely.

Methods

Between 2000 and 2010, >1200 patients were evaluated in Mayo Clinic’s Long QT Syndrome Clinic and 613 patients were diagnosed or confirmed to have LQTS. The first LCSD for LQTS at Mayo Clinic was performed in November 2005. During this time period, 54 of 613 LQTS patients (8.8%) have had a LCSD performed. In this study, approved by Mayo Clinic’s Institutional Review Board, we retrospectively reviewed the electronic medical record for 52 patients with...
LQTSs who underwent LCSD at our institution from November 2005 through December 2010 and had ≥2-year follow-up post LCSD. There were 2 additional patients who underwent LCSD during this time period but were lost to follow-up and therefore excluded from the analysis. Clinical follow-up was censored at December 1, 2012, for analyses. All QTcs were calculated using Bazett formula. Only patients who received denervation therapy at Mayo Clinic were included in this study.

All procedures were performed using the minimally invasive, video-assisted thoracoscopic technique that has been described previously. Briefly, using a video-assisted transthoracic approach, the left-sided sympathetic ganglia were identified. Subsequently, the sympathetic chain was exposed from T4 to T1 and the ganglia/sympathetic chain was removed en bloc, including the lower half of the left stellate ganglion (C7/T1), which was divided along the anatomic fusion between its upper and lower poles. Postoperative chest x-ray was performed to confirm the absence of significant pneumothorax.

Each electronic medical record was reviewed for initial diagnosis, sentinel and subsequent events, genotype, and indications for LCSD. After LCSD, the records were reviewed for follow-up data, complications (short and long-term), and events post procedure. All patients were genotyped for mutations in the LQTS-associated genes by commercial genetic testing. After their comprehensive clinical assessment by a single LQTS specialist (M.J.A.), patients were classified clinically as being at high, moderate, or low risk for subsequent cardiac events. In terms of this qualitative risk classification, high-risk patients included those with either (1) a history of aborted cardiac arrest; (2) Bceans such as an appropriate ventricular fibrillation-terminating ICD shock or arrhythmic syncope, seizures, or aborted cardiac arrest; or (3) asymptomatic postpubertal LQTS females with a QTc ≥500 ms. Moderate risk patients included those with either (1) a history of arrhythmic (by documentation or by description) syncope/seizures; (2) asymptomatic with QTc ≥500 ms regardless of age and genotype besides postpubertal LQTS females; and (3) asymptomatic prepubertal boys or postpubertal females with QTc ≥480 ms who are not LQT1. Comparatively low-risk status was assigned to asymptomatic prepubertal girls and postpubertal males with QTc <480 ms regardless of genotype.

Most patients were treated with nadolol or propranolol β-blockers. Nadolol was first-line therapy in adults and adolescents, whereas liquid propranolol was considered first-line therapy in infants and young children. Patients were deemed β-blocker intolerant if they were unable to tolerate either of the preferred β-blockers at the prescribed dose because of side effects, including fatigue, hypotension, bradycardia, lightheadedness, and mood swings. Often, trials with both β-blockers at multiple doses were attempted before designating a patient β-blocker intolerant. Some patients deemed β-blocker intolerant continued to use β-blockers albeit at a potentially subtherapeutic dose of <0.5 mg/kg per day (nadolol) or <2 mg/kg per day (propranolol) being identified as their maximum, acceptably tolerated dose. Four of these patients, who chose denervation therapy because of drug-related side effects that were deemed unacceptable, have chosen LCSD monotherapy and are not on any LQTS-directed medications.

For this analysis, a BCE was defined as either (1) an appropriate ventricular fibrillation-terminating ICD shock or (2) arrhythmic syncope, seizures, or aborted cardiac arrest after LCSD. Patients with either an increase in cardiac events post procedure or those without a decrease in events were considered therapeutic nonresponders, and their genotypes and phenotypes were scrutinized extensively for the purpose of this study.

Statistical analysis was performed using JMP 8.0 statistical software (JMP 8.0, SAS Institute Inc. Cary, NC) using Student t test for continuous variables and Fisher exact test for nominal values in subgroup comparisons. Correction for multiple comparisons was performed using Bonferroni correction. Effect of genotype was calculated using ANOVA. Differences in incidence of cardiac events pre and post LCSD were tested using McNemar test for matched pairs. A P value of <0.05 was considered statistically significant. Cumulative event-free survival was calculated using Kaplan–Meier curves and tested in subgroups by log-rank for trend. For this analysis, time was calculated to the first BCE post LCSD and data are displayed as cumulative event-free survival.

Results

Between November 2005 and December 2010, 54 patients with LQTS underwent videoscopic LCSD at Mayo Clinic and were enrolled in our current study; however, 2 patients were lost to follow-up and were excluded from further analyses. Demographics of this study cohort are summarized in Table 1 (first column) with a flow-chart showing the different subgroups in Figure 1. There were 24 males (46%), average age at diagnosis was 10.0±10 years and mean baseline QTc before LCSD procedure was 528±74 ms. Thirty-three patients (63%) underwent LCSD as primary prevention, whereas the remaining 19 patients (37%) underwent LCSD as secondary prevention. Sixty-three percent of patients were considered at high risk for a potentially lethal arrhythmia. The main clinical indications for LCSD were β-blocker intolerance (33%), assessment of severe/high-risk LQTS (25%), a BCE while on medication (19%), or patients in whom additional protection was felt to be necessary (23%). The average age at surgery was 14.1±10 years and the mean follow-up post LCSD was 3.6±1.3 years (range, 2–6.3 years). Ninety-two percent of patients were genotype positive for ≥1 mutations in the 3 canonical LQTS-causing genes: KCNQ1 (LQT1), KCNH2 (LQT2), or SCN5A (LQT3), with LQT1 as the most common genotype (43%).

Overall, of 52 patients undergoing LCSD, 12 patients (23%) have experienced ≥1 BCE post LCSD so far. Compared with 34 of 52 patients who had cardiac events pre LCSD, this shows a significant reduction of patients with cardiac events post procedure (P<0.001). Of the 34 patients that had cardiac events pre LCSD, 5 patients (15%) have not experienced any discernible reduction in cardiac events post LCSD. Conversely, among the 29 previously symptomatic patients with a reduction of cardiac events post LCSD, 79% of them have had no BCEs so far (Figure 2). The mean time to first BCE was 1.7±1.6 years with the shortest interval from surgery to their first BCE being 4 days and the longest 4.4 years.

Primary Versus Secondary Prevention

Looking at prevention strategies, all BCEs occurred in patients undergoing LCSD for secondary prevention (Table 1, middle columns). Ninety-five percent of these patients (18/19) were classified clinically as high risk, compared with 15 (45%) high-risk patients in the primary prevention subgroup (P<0.001). Patients in the secondary prevention subgroup were also significantly younger at diagnosis, had a significantly higher baseline QTc, were more likely to have an ICD pre procedure, and were more likely to experience a BCE while on pharmacotherapy before their LCSD (Table 1).

LCSD Surgical Complications

Of the 52 patients, there were no intraoperative or postoperative arrhythmias. A small, spontaneously resolving pneumothorax was observed in 3 patients, and 4 patients had a transient left eyelid ptosis with resolution by 3 months post LCSD.

Analysis of BCEs

Twelve patients (23%) experienced ≥1 BCE post LCSD (Table 1). Overall, patients experiencing a BCE had a
significantly higher baseline QTc (597±106 versus 507±45 ms; \(P=0.04\)), were more likely to have an ICD pre procedure (83% versus 15%, respectively; \(P<0.001\)), and were more likely to have received ICD shocks pre procedure (100% versus 22%; \(P<0.001\)).

There were no BCEs seen in patients with single mutation LQT1, whereas all 4 patients with neonatally expressed, malignant LQT3 experienced ≥1 post-LCSD BCE (Figure 3).

Importantly, none of the LCSD patients who underwent LCSD for \(\beta\)-blocker intolerance have experienced a BCE to date. After correction for multiple comparisons, specific LQT diagnosis, risk classification, and indication were still significantly different between patients with and without BCE post LCSD (\(P<0.05\)).

### \(\beta\)-Blocker Intolerance

Overall, 17 patients (33%; 14 males) underwent LCSD for \(\beta\)-blocker intolerance as their primary indication. This included patients who either experienced too many side effects from their medication or were noncompliant with their prescriptions. Compared with the patients who underwent LCSD for another indication, patients designated as \(\beta\)-blocker intolerant were significantly older at diagnosis (15.6±8 versus 7.3±9 years; \(P=0.001\)), older at LCSD (20.7±8 versus 11.1±9 years; \(P<0.001\)), and had lower QTc pre LCSD (492.5±32 versus 540.6±13 ms; \(P=0.003\), data not shown).

Only 4 of these 17 patients were classified clinically as high risk and the remainder (13/17) low risk, whereas for the other 35 patients, 29 were considered as high risk (\(P<0.001\)). Although 6 of these 17 \(\beta\)-blocker intolerant patients (36%) had experienced ≥1 cardiac events pre LCSD, none have experienced a BCE to date (Figure 4). In contrast, of the other 35 patients, 28 (80%) had cardiac events pre LCSD, and 12 (34%) have experienced a BCE (Figure 4; \(P<0.05\)).

Of the 17 patients with \(\beta\)-blocker intolerance, 12 (71%) have been able to decrease their \(\beta\)-blocker dose post LCSD to a more tolerable dosage (albeit likely insufficiently therapeutic by itself, <0.5 mg/kg per day nadolol or <2 mg/kg per day propranolol), and 4 have elected to rely on LCSD as monotherapy. One patient did not change the \(\beta\)-blocker dose; however, it was already prescribed at a suboptimal dose as the full dose was tolerated poorly.

### Event-Free Survival

Event-free survival from BCEs for the complete cohort is shown in Figure 5A. Overall, for those with ≥5 years of...
available follow-up, ≈60% have experienced 1 BCE. Looking at the different indications, patients with a recent cardiac event pre LCSD or severe/high-risk LQTS are most likely to experience a breakthrough post LCSD (Figure 5B; \( P = 0.001 \)). As discussed previously, patients with β-blocker intolerance did not experience any BCEs post LCSD (Figure 5B). When grouping patients based on the number of cardiac events pre LCSD (0, 1–5, 6–10, or >10 events), we see that patients with >10 events pre LCSD do significantly worse post LCSD compared with patients in the other subgroups (\( P < 0.001 \); Figure 5C).

**Phenotype of Therapeutic Nonresponders/Denervation Failures**

Of the 12 patients with ≥1 BCE post LCSD, 5 patients had no measureable attenuation in LQTS-triggered cardiac events and were deemed therapeutic nonresponders. The phenotypic characteristics of these patients are summarized in Table 2. Four of the 5 patients were males. Three of the cases had mutations in SCN5A (LQT3), whereas the other 2 had multiple mutations in KCNQ1 (without deafness). All 5 denervation nonresponders had phenotypically extreme LQTS with a mean QTc of 691 ms (range, 600–730 ms), and all 5 were diagnosed with LQTS as infants. Each of these patients underwent LCSD as secondary prevention and was classified as high risk before the procedure. Two patients (cases 2 and 5) have had an additional right cardiac sympathetic denervation performed in an attempt to provide sufficient protection to avoid or delay cardiac transplantation. A more detailed description of each patient’s phenotype and clinical course categorized as nonresponder can be found in the online-only Data Supplement.

**Discussion**

The role of the autonomic nervous system, ventricular arrhythmogenesis, and concordantly LCSD’s antifibrillatory effect have been well described.\(^9\)\(^–\)\(^11\) Previous studies on groups of patients undergoing LCSD have shown it is a safe and effective treatment option to reduce life-threatening ventricular arrhythmias in patients with heritable channelopathies\(^4\)\(^,\)\(^6\)\(^,\)\(^12\) and possibly even hypertrophic cardiomyopathy.\(^13\)\(^,\)\(^14\) Furthermore, ≈30% of denervated LQTS patients had a ≥30 ms reduction in their QTc post LCSD in 1 series.\(^8\)

In their first series of 85 patients (73 females), Schwartz et al\(^12\) reported a significant decrease in cardiac event rates from 99% to 45% (\( P < 0.001 \)) and 5-year survival rate of 94%. In their follow-up study of 147 patients with LQTS, an ≈90% reduction in cardiac event rates was observed.\(^8\) In our initial experience in 20 patients with a heritable channelopathy (mostly LQTS), there was a reduction of cardiac events in 9 of 12 patients who received therapy because of secondary

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**Figure 1.** Flow-chart showing the study cohort and the breakdown of different subgroups analyzed. Of 54 patients undergoing left cardiac sympathetic denervation (LCSD) during the study period, 2 were lost to follow-up. The subsets were analyzed by indication (primary vs secondary prevention), β-blocker intolerance, or occurrence of ≥1 breakthrough cardiac event (BCE) post LCSD.

**Figure 2.** Diagram showing patients grouped by number of cardiac events pre and post left cardiac sympathetic denervation (LCSD). Shading assigned to each of the 3 groups before LCSD for number of events demonstrates the direction shift of number of events post LCSD.

**Figure 3.** Graph demonstrating number of patients with breakthrough events by genotype. No breakthroughs were observed in patients with LQT1, whereas the 4 patients with LQT3 have each experienced ≥1 breakthrough event. BCE indicates breakthrough cardiac event; and G−/P+, genotype negative, phenotype positive.

**Figure 4.** Graph demonstrating breakthrough events for number of patients with or without β-blocker intolerance. LCSD indicates left cardiac sympathetic denervation.
prevention, whereas none of the patients undergoing LCSD for primary prevention had an event post procedure.4 Overall, our current data showed similar post-LCSD success with 85% of patients experiencing a reduction of cardiac events post LCSD (Figure 2). However, although all these studies focus on the overall success of LCSD, the phenotype of patients who experience BCEs has not been examined. We, therefore, set out to evaluate the phenotype of those patients experiencing post-LCSD breakthroughs and evaluate LCSD as an alternative treatment option for patients with β-blocker intolerance. Here, 12 of 52 patients have experienced ≥1 BCE post LCSD and 5 patients (~15%) had no discernible attenuation in LQTS-triggered events after denervation (nonresponders).

Our analysis showed that patients who experienced a BCE had a significantly higher baseline QTc, were more likely to have an ICD pre procedure, and were more likely to have received ICD shocks pre procedure compared with patients without a breakthrough event. As these comparisons already indicate, all of these patients were classified as high risk before the procedure, whereas <60% of the heretofore nonbreakthrough patients were considered high risk. Furthermore, patients receiving denervation therapy as secondary prevention were more likely to have a BCE compared with patients having the procedure done for primary prevention (Table 1), demonstrating that the highly arrhythmogenic phenotype of patients with extreme cases of LQTS cannot be eliminated by LCSD alone.

In our study, none of the type 1 LQTS patients (ie, patients with single mutations in KCNQ1) had a BCE, whereas all 4 of the type 3 LQTS patients had a postdenervation BCE (Figure 3). Although small in numbers, these results might be explained by the different pathogenic processes underlying the phenotype of patients with LQT1 and LQT3 and mirror the clinical results observed regarding the differential efficacy of β-blockers. Physiologically, the β-adrenergic effect of the sympathetic nervous system on the heart is propagated primarily through activation of the delayed rectifier potassium channels (Iks channels). Mutations in Iks channels, such as the Kv7.1 potassium channel in patients with LQT1, impair QT shortening in response to a heart rate increase with increased sympathetic activity leading to a propensity of cardiac events during, for example, exercise.

LQT3 is characterized by mutations in the SCN5A-encoded α-subunit of the cardiac Nav1.5 sodium channel, and these patients do not typically have events during exercise, but during rest. Furthermore, the poorer results in LQT3 patients might be explained partially by the studies into the efficacy of β-blockers in LQTS.15–17 Exerting their activity on blocking β-receptors, potassium currents and sympathetic activity, various clinical studies have shown β-blockers to be far more effective in patients with LQT1 compared with LQT3,15–17 suggesting that proarrhythmic triggers in LQT3 might lie outside the sympathetic chain. However, in contrast to our results, Schwartz et al6 reported that among their 51 genotyped patients, there were no BCEs among the subset with LQT3. Notably our LQT3 patients were much younger and exhibited a much more aggressive LQTS phenotype than their patients. Akin to our observations, all nonresponders had their cardiac event in the first year of life, emphasizing the severity of their disease and propensity to be a nonresponder to any therapy.6,18

Interestingly, of the 17 patients who underwent LCSD for β-blocker intolerance, none have thus far experienced a BCE. Furthermore, most of these patients have decreased their β-blocker dosage or even discontinued its use. These data show prophylactic LCSD may provide an acceptable, quality of life improving alternative to an ICD in these patients thereby...
providing sufficient LQTS protection without the intolerable side effects from their \( \beta \)-blockers. However, one must be very prudent in patient selection and LCSD should certainly not be viewed as curative or an ICD alternative in high-risk patients. More data and longer follow-up are needed before LCSD could be considered as an alternative to \( \beta \)-blocker therapy in the appropriately selected low-to-moderate risk patient.

Underscoring the evidence that LCSD cannot and must not be viewed as curative, 5 patients (10%) were therapeutic non-responders or denervation failures. However, their expressed LQTS phenotypes were clearly extreme. Four of the 5 were diagnosed during the first week of life and all exhibited extreme QT prolongation. Whether or not the addition of right-sided cardiac denervation will help achieve adequate arrhythmia suppression in those patients with extreme LQTS expressivity refractory to pharmacotherapy and LCSD will require further investigation.

**Limitations**

Inherent to the nature of retrospective clinical research, our current study has some limitations. First of all, because of the nature of Mayo Clinic as a tertiary referral center, ICD interrogations are not universally available. Therefore, data on the effect of \( \beta \)-blockers (pre and post procedure) or effect of LCSD on mitigation of adrenergic surges or efficacy of sympathetic blockade using the ICD data were not available. A temporary ganglion block pre LCSD to test these effects was not performed in our patients. Lastly, although in our study all 4 patients with LQT3 showed poor response to LCSD, the small number of patients in this subset does not provide sufficient evidence to suggest that there is no role for denervation therapy in LQT3. Future studies on a larger cohort of patients with LQT3 patients with additional follow-up should be able to demonstrate whether there is LQT3-specific inferiority to denervation’s antifibrillatory effect.

**Conclusions**

LCSD is an important therapeutic option for patients with LQTS. In our cohort akin to previous observations, a reduction in cardiac events was achieved in 85% of patients. Analysis of patients who have had BCEs suggests that LCSD must not be viewed as curative or as an ICD alternative for high-risk patients. Although a marked reduction in cardiac events is usually seen after LCSD from an overall perspective,≈50% of high-risk LQTS patients have experienced ≥1 post-LCSD BCE and patients with extremely malignant LQTS might not be responsive to left-sided denervation therapy. Among appropriately risk-stratified patients, a prophylactic LCSD, rather than a prophylactic ICD, may represent a robust therapeutic option for patients with unacceptable \( \beta \)-blocker-related side effects.

**Disclosures**

Dr Ackerman is a consultant for Transgenomic (approved by Mayo Clinic’s Medical-Industry Relations Office and Conflict of Interests Review Board). In addition, cardiac channel gene screen and knowledge relating to long QT genetic testing license agreements, resulting in consideration and royalty payments, were established between Genaissance Pharmaceuticals (then PGxHealth, and now Transgenomic) and Mayo Medical Ventures (now Mayo Clinic Health Solutions) in 2004. Dr Ackerman is also a consultant for Boston Scientific Corporation, Medtronic, and St. Jude Medical Inc.
However, none of these entities provided financial support for this study. The other authors report no conflict.

References


CLINICAL PERSPECTIVE

Left cardiac sympathetic denervation is a therapeutic option for patients with long QT syndrome who have recurrent arrhythmias, despite β-blockers or when β-blockers are not tolerated. The prevalence and determinants of breakthrough cardiac events post left cardiac sympathetic denervation are unknown. We report our series of 52 patients with long QT syndrome who underwent left cardiac sympathetic denervation with a special focus on those patients who experienced ≥1 breakthrough cardiac event after their left cardiac sympathetic denervation. Although a marked reduction of cardiac events is seen for the cohort as a whole, ≥50% of the high-risk patients have ≥1 breakthrough cardiac event and 10% do not have a reduction in cardiac events. Thus, cardiac denervation therapy is not curative. However, breakthrough events were seen mostly in predictably high-risk long QT syndrome patients with genotypes other than LQT1.
Left Cardiac Sympathetic Denervation in Long QT Syndrome: Analysis of Therapeutic Nonresponders
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Description of patients classified as ‘non-responders’

There were two cases with double mutations in KCNQ1 (Case 1 and 2). One patient (Case 1) was homozygous for R174C-KCNQ1 but did not have concomitant deafness. His family history was negative for LQTS or SCD and the family history was negative for consanguinity. Although a dramatic decrease in ICD-shocks was observed initially, he had several VF-storms several months later. A right sided cardiac sympathetic denervation (RCSD), to complete a bilateral sympathectomy, was advised but the family declined. About 14 months after LCSD, he was admitted to the emergency department after having several episodes of symptomatic VT and after 2 periods of asystole, the child expired at age 3 of multiple organ failure. The second patient (Case 2) was a boy diagnosed with compound LQT1 at 1 month of age with an L191fs/90 (maternal) and V524G (paternal) KCNQ1-mutation without concomitant deafness. Both parents are asymptomatic with borderline QTc and he has two brothers that are asymptomatic, one heterozygous for the frameshift mutation and the other heterozygous for the missense mutation. He has one sister who is compound heterozygous for both variants with symptomatic LQTS albeit not as severe as this patient. Our patient received his ICD in 2007 after a breakthrough cardiac event while on nadolol. Following an event-free period of 3 years, he received 5 VF-terminating therapies after which LCSD was performed. Within 6 months however, he received two additional VF-terminating shocks, which led to the decision to perform a RSCD. After 1 event-free year, he recently received a VF-terminating shock while status post both LCSD and RCSD and compliant on high dose nadolol.

The arrhythmic phenotype of Case 3, a now 4 year-old boy, has shown to be extremely malignant. Diagnosed with LQT3 (F1473C-SCN5A; QTc 687 ms) after hospitalization for necrotizing enterocolitis, he underwent LCSD at three months of age after 2 previous ICD shocks. Since his
procedure, he has had hundreds of recorded arrhythmias and over 90 appropriate VF/VT-terminating ICD shocks while on high dose mexiletine and propranolol.

**Case 4**, a now 5 year-old boy, presented at birth with 2:1 AV-block with extreme QT-prolongation. He was genotype positive for a I397F mutation in SCN5A (LQT3). He was implanted with a pacemaker and treated with propranolol until he experienced an out-of-hospital cardiac arrest (OHCA) while sleeping at age 7 months. He was defibrillated externally and an ICD was implanted. As the patient is adopted, his family history is largely unknown. After his ICD implantation, he had multiple VF-terminating shocks, after which LCSD was performed. Despite LCSD and beta blocker therapy, he has had multiple breakthrough events, and either RCSD or cardiac transplant are being considered currently.

Lastly, **case 5** is now a 17-year-old woman, diagnosed at birth with LQT3 (R1623Q-SCN5A) and 2:1 AV-block with QTc values ranging between 600 – 700 ms for which she received a pacemaker and treatment with a beta blocker. Shortly after dismissal home, she had an OHCA at 6 weeks of age. At age 4, she received an ICD and between age 4 and 16, she had approximately 20 VF-terminating ICD shocks. Because of these breakthrough events and mexiletine-CNS-toxicity (including hallucinations) affecting her quality of life, LCSD was performed. She, however, continued having arrhythmias and drug-induced hallucinations after which RCSD and VF-ablation were performed leading to a decrease in arrhythmia burden. However, because of persistent unwanted side effects from her LQT3-directed pharmacotherapies and concerns of possible recurrences, she received a cardiac transplant elsewhere.