Long QT Syndrome in Children in the Era of Implantable Defibrillators

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Objectives
We sought to assess the spectrum and outcome of young long QT syndrome (LQTS) patients, addressing treatment including device indications, risks, and benefits.

Background
Long QT syndrome has a phenotype ranging from asymptomatic electrocardiogram (ECG) abnormalities to sudden death. Treatments include beta-blockers and device implantation in high-risk individuals. Despite genetic testing, accurate risk stratification remains challenging.

Methods
A database search at 3 institutions identified all pediatric LQTS patients. Records were reviewed for demographics, criteria for diagnosis, treatment, follow-up, and ECG and device data.

Results
We identified 128 patients ages 8.0 ± 5.4 years with QTc of 487 ± 39 ms and follow-up of 4.4 ± 3.5 years. Most were diagnosed because of an abnormal ECG in a patient with a family history (53%). Genetic mutations were identified in 51 patients. Beta-blockers were used in 126 (98%) and pacemaker/implantable cardioverter-defibrillator implantation in 27 (21%) patients, usually because of symptoms despite use of beta-blockers. Pacing was common; 22% received an appropriate shock but device-related re-intervention occurred in 48%. Device patients had longer QTc intervals (p = 0.03) and more symptoms (p < 0.001). No one with an isolated KCNQ1 and all patients with an SCN5A mutation had device implantation. During the study period, there were 2 deaths.

Conclusions
Long QT syndrome without symptoms is increasingly recognized as family members are screened. Evaluation of this minimally symptomatic population offers an evolving understanding of LQTS. Previous studies of highly symptomatic patients were more worrisome. In the era of genetic testing and device implantation, overall mortality is low with treatment. Device therapy, although effective, is not without complications and should be reserved for high-risk patients. (J Am Coll Cardiol 2007;50:1335–40) © 2007 by the American College of Cardiology Foundation

Long QT syndrome (LQTS) is the prototype channelopathy. With over 600 disease-causing mutations in cardiac ion channel genes, LQTS is thought to affect at least 1 in 5,000 people. The LQTS phenotype is variable, ranging from asymptomatic electrocardiogram (ECG) repolarization abnormalities to sudden death. There are several variables that have been associated with a high risk of sudden death, including young age (1,2), the presence of a sodium channel mutation (SCN5A) (3), a markedly prolonged QT interval (4), the Jervell and Lange-Nielsen genotype (5), and other compound mutations (6). The ability to determine the specific genetic abnormality has permitted correlations with phenotype that may improve risk stratification. Yet, at present, genetic testing is largely limited to research protocols and a single commercial laboratory. Despite an increase in genetic testing, precise risk stratification is not possible.

As the awareness of LQTS increases, more cases are identified; many asymptomatic cases are brought to medical attention as the result of family screening, further confounding risk stratification. The variables previously described to be associated with high risk may not, therefore, apply to this growing population.

Although genetic testing and our understanding of the mechanism of LQTS have increased dramatically, the therapy in LQTS has remained empiric. Beta-blockers form the mainstay of therapy in all patients, whereas high-risk patients now receive implantable cardioverter-defibrillators (ICDs). Decisions concerning appropriate therapy must be undertaken with a comprehensive understanding of the variable phenotype and genotype.
Young patients with LQTS are thought to be at greater risk when compared with adults, and adolescents represent the highest risk group (2). As a result, more aggressive treatment has been advocated in this population (7). We set out to evaluate a large cohort of children with LQTS to better understand LQTS and improve risk stratification in the era of family screening, genetic diagnosis, and ICD implantation.

Methods
Population. After institutional review board approval was obtained from the 3 participating institutions, pediatric cardiology database searches identified all patients 18 years of age or younger diagnosed with LQTS from January 1990 to June 2006. Demographic data, personal and family history, ECG data, and genetic diagnosis, when available, were ascertained. Follow-up was closed on August 1, 2006, or at the patient’s last recorded cardiology clinic visit. Five patients had not attended follow-up appointments in more than 2 years and could not be contacted concerning their condition. Although their medication compliance and clinical status are unknown, the social security death records were searched to confirm that there were no deaths reported in this group. The initial baseline, un-paced 12-lead ECG before therapy, was used to calculate the corrected QT interval using the formula of Bazett (8). Genetic analyses were performed in established laboratories, including both research and commercial facilities. Patients were frequently assessed with exercise testing, although this was not systematic. The use of epinephrine challenge was uncommon.

The proband was defined as the first patient in a family diagnosed with LQTS; the term nonproband was used to describe all other relatives regardless of symptoms or health status.

Device patients. Device implantation indications, programming data, antitachycardia therapies, complications, and revisions were noted. The percentage of time paced and appropriate and inappropriate ICD discharges were reviewed. Device patients were compared with those without devices.

Statistical analyses. Quantitative variables are presented as mean ± SD and categorical variables as percentages. Student t test was used to compare continuous data and the chi-square or Fisher exact test for categorical data. Kaplan-Meier analysis was used to assess survival with differences between groups determined by log-rank test. A p value of <0.05 was considered significant.

Results
Population. A total of 128 patients were identified with LQTS from 91 families. These included 52 (41%) probands and 76 nonproband. There were 66 (52%) female patients. The mean age at diagnosis was 8.0 ± 5.4 years. The QTc was 487 ± 39 ms, and the length of follow-up was 4.4 ± 3.5 years. Probands had significantly longer QTc intervals (495 ± 42 ms) when compared with nonprobands (481 ± 37 ms, p = 0.04) and were older at diagnosis (9.6 ± 5.1 years vs. 6.8 ± 5.4 years, p = 0.003). The most common reason for diagnosis was an abnormal screening ECG in the setting of a positive family history, as shown in Figure 1. Seven patients who presented for evaluation acknowledged a family history of LQTS but did not seek medical attention until they experienced syncope. They were included in the nonproband group.

Genetic testing. Genetic testing has been performed in 72 patients (56%) and has identified an abnormality in 51 (40%) patients (Fig. 2). There were 3 patients with genetic test results that were negative for known mutations, and test results are pending in 18. A KCNQ1 mutation was the most common defect identified. A single proband with multiple syncopal events and a markedly prolonged QTc interval was identified as a compound heterozygote with both KCNQ1 and SCN5A mutations. In those with positive genetic test results, there were 6 with borderline (450 to 460 ms) QTc prolongation and 1 with a normal QTc at 430 ms; none had an SCN5A mutation.

Therapy. In this population, 126 (98%) patients were on beta-blocker therapy. One patient was diagnosed after her sudden death when a prior ECG and family history were reviewed. A second patient with an SCN5A mutation and an ICD was not treated with a beta-blocker. Beta-blocker therapy included nadolol in most patients, with propranolol and atenolol used less often. Because of described treatment failures (9), the investigators have decreased the use of atenolol. Adequacy of beta-blockade was routinely assessed with 12-lead ECG, Holter monitoring in young patients, and Acronyms

- ECG = electrocardiogram
- ICD = implantable cardioverter-defibrillator
- LQTS = long QT syndrome
- TdP = torsades de pointes
with at least 1 inappropriate ICD discharge, including 2 patients with both. Appropriate ICD discharges occurred during exertion in 3 patients, including 2 brothers who were fighting with one another at the time of their nearly simultaneous shocks. Although these 2 have had multiple appropriate shocks during periods of exercise, no patient has had a classic electrical storm with multiple consecutive shocks. The other 2 patients with appropriate discharges had events during rest. Thus, 5 of 23 (22%) patients have received appropriate ICD therapy, with a mean time to first appropriate shock of 18 ± 22 months.

When the ICD patients with an appropriate shock were compared with those without, there was no difference in age, QTc interval, length of follow-up, or length of time with a device. Only 2 of the patients with appropriate shocks have been gene tested, and both have a KCNH2 mutation. Conversely, 4 patients with this mutation have not had appropriate shocks and no one with a known SCNSA mutation has had an appropriate ICD discharge.

Of the 13 patients with a device implanted for syncope despite beta-blocker therapy, 9 had no further symptoms, 3 had appropriate ICD discharges, and 1 with a pacemaker had continued syncope and underwent upgrade to an ICD. She has had no ICD discharges or further syncope (Fig. 4). There were 4 patients who underwent device implantation because of documented ventricular arrhythmias (2 ICDs, 2 pacemakers). In this group, 1 ICD patient had no further symptoms and the other had an appropriate ICD discharge. One patient with a pacemaker underwent a change to an ICD after a documented ventricular fibrillation arrest. The

and exercise testing in older children. Both mexiletine and a beta-blocker were used in 2 patients.

**Device therapy.** Implantation indications varied little between centers (Fig. 3). All 3 centers recommended implantation for documented ventricular tachycardia or torsades de pointes (TdP), syncope despite beta-blocker therapy, presentation with resuscitated sudden death, and identification of an SCN5A mutation. Although 3 patients had ICDs implanted because of a family history of sudden death, there was not a consensus among participating electrophysiologists concerning this indication.

A total of 27 patients had devices placed, including 8 with epicardial (4 pacemakers, 4 ICDs) and 19 with endocardial systems (4 pacemakers, 15 ICDs). The age at implantation of a device was 9.4 ± 5.4 years. Children with epicardial devices were 5 years of age or younger. There were 20 (74%) patients with dual-chamber devices and 7 (26%) with single-chamber ventricular devices. Device programming was done according to 2 strategies: 1) the shock box approach, single-chamber demand pacing at a lower rate of 40 to 50 beats/min (8 patients, 30%); or 2) the rate support approach, in which a higher-than-age-appropriate resting heart rate was chosen for the prevention of pauses (19 patients, 70%).

Indications for pacemaker implantation were syncope despite beta-blocker therapy (6 patients), ventricular arrhythmias despite beta-blocker therapy (1 patient), and 2:1 atrioventricular block (1 patient) (Fig. 3). Four patients with pacemakers underwent a change to an ICD: 3 had documented ventricular arrhythmias despite pacing, and 1 upgrade was performed at the time of generator change in a patient with medication noncompliance. An ICD was the initial device therapy in 19 patients. Therefore, a total of 23 patients ultimately had ICD implantation, whereas 4 remained with a pacemaker.

Based on device interrogation data, 63% of patients had more than 30% of heart beats paced. There were 5 patients who had at least 1 appropriate ICD discharge and 4 patients with at least 1 inappropriate ICD discharge, including 2 patients with both. Appropriate ICD discharges occurred during exertion in 3 patients, including 2 brothers who were fighting with one another at the time of their nearly simultaneous shocks. Although these 2 have had multiple appropriate shocks during periods of exercise, no patient has had a classic electrical storm with multiple consecutive shocks. The other 2 patients with appropriate discharges had events during rest. Thus, 5 of 23 (22%) patients have received appropriate ICD therapy, with a mean time to first appropriate shock of 18 ± 22 months.

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other pacemaker patient died suddenly in infancy on beta-blocker therapy before the accepted use of ICDs in small infants. Of the 3 patients with ICD placement after presentation with resuscitated sudden death, none had further symptoms or ICD shocks although arrhythmias were documented. There were 2 patients in whom ICD interrogation disclosed a spontaneously terminating ventricular tachycardia episode.

Inappropriate ICD shocks were seen in 4 of 23 (17%) patients: 3 for sinus tachycardia during exertion, and 1, a child with an SCN5A mutation, had a shock with atrial fibrillation. All were receiving beta-blockers and all had dual-chamber devices; no inappropriate shocks were seen in the single-chamber device patients. There were no inappropriate shocks because of lead fracture or T-wave oversensing.

Over a mean follow-up of 3.5 ± 2.3 years, 13 patients (48%) required re-intervention related to their device. This includes device recalls in 5 (2 with associated upgrade to dual chamber device), upgrade from a pacemaker to an ICD in 4, and a single re-intervention each for battery depletion, lead repositioning, lead fracture, and infection.

Device patients had longer corrected QT intervals (p = 0.03) and were more likely to have symptoms than the group without devices (p < 0.001) (Table 1). Interestingly, patients with devices were not more likely to be probands, and their survival did not differ from that of patients without devices (Fig. 5).

No patient with a known, isolated KCNQ1 mutation had an ICD (Fig. 6), but all 5 patients known to have an SCN5A mutation did. There was no association between device placement and implementation of genetic testing.

In our patients there were 2 deaths (2%). A young woman died before diagnosis and without treatment. Review of her previous ECG and evaluation and genetic testing of family members confirmed a KCNQ1 mutation. The other death was an infant with 2:1 AV block who died suddenly despite a pacemaker and beta-blocker therapy. Neither death occurred during exertion.

Discussion

Long QT syndrome is a genotypically and phenotypically heterogeneous disease. Despite the wide range of clinical manifestations, therapeutic options are limited and include beta-blockade, mexiletine, pacemakers, and ICD implantation in addition to sports restrictions and avoidance of medications that lengthen repolarization.

Decisions concerning candidacy for device therapy have not been standardized (10) and remain medically and psychologically challenging in young patients (11,12).

Table 1  Comparison of Long QT Syndrome Patients With and Without a Device

<table>
<thead>
<tr>
<th></th>
<th>Device</th>
<th>No Device</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>Age at diagnosis (yrs)</td>
<td>7.3 ± 5.7</td>
<td>8.1 ± 5.3</td>
<td>NS</td>
</tr>
<tr>
<td>Length of follow-up (yrs)</td>
<td>4.8 ± 3.8</td>
<td>4.1 ± 3.3</td>
<td>NS</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>502 ± 53</td>
<td>483 ± 33</td>
<td>0.03</td>
</tr>
<tr>
<td>(+) syncope (%)</td>
<td>81</td>
<td>37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(+) proband (%)</td>
<td>52</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>(+) family history (%)</td>
<td>73</td>
<td>75</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figure 4  Outcomes in Pacemaker and ICD Patients

There were 8 patients in whom a pacemaker was initially implanted. In this group there was 1 death, and 4 patients underwent upgrade to an implantable cardioverter-defibrillator (ICD), 3 after documented ventricular tachycardia (VT) or ventricular fibrillation (VF). A single asymptomatic patient underwent an upgrade to an ICD at the time of a generator change because of concerns about compliance with beta-blocker therapy. There were 19 patients who underwent an ICD implantation as initial device therapy. Appropriate shocks have occurred in 5 patients, and inappropriate shocks in 4 patients. Sixteen ICD patients have not had a shock.

Figure 5  Kaplan-Meier Survival Curve of Patients With and Without a Device

A shown in this Kaplan-Meier graph, survival was not different in patients with and without devices. The 15-year survival was >90% in both groups.
Technical advances such as smaller generator size and subcutaneous high-voltage electrodes have helped decrease the role of size in the selection of device therapy. Although use of a pacemaker in smaller children with later upgrade to an ICD proved an effective option in some of our patients, the sudden death of 1 infant underscores the possible consequences of pacing without an ICD. The decision to use device therapy in an infant is an amalgam of 3 components: patient size, perceived risk of events, and technical limitations. Once the technical disadvantages of an ICD are overcome, this therapy should be selected over pacing. The rate of appropriate shocks (22%) and the use of bradycardia functions of the devices show their value for selected LQTS patients.

Growing children, in whom a lifetime of device therapy is required, are at greater risk for device-related complications. Faster sinus rates increase the risk of inappropriate ICD discharges (12,13) and associated medical and psychological impact. The frequency of re-intervention and the inappropriate shocks are persuasive evidence against a more aggressive implanting approach.

Patients in our series with devices were genetically distinct: no patient identified with an isolated KCNQ1 mutation had a device, whereas all patients with a known SCN5A mutation have ICDs. Selection of appropriate device recipients remains challenging but should be limited to high-risk patients unlikely to respond to or having failed beta-blocker therapy.

Causes of individual clinical events are incompletely understood and vary with genotype (3,6). Although young patients are thought to have an increased risk of sudden death (2), we found that mortality was low in this cohort. Our study group is unique in that it represents a young population, often identified in the absence of symptoms. Early identification, intervention with beta-blocker therapy, and necessary restrictions may underlie the low mortality.

Increasing awareness of medication interactions may be a protective factor in the current era. Use of beta-blocker therapy has been associated with a reduced risk of sudden death and aborted sudden death in high-risk individuals (2), but has not proven as effective in eliminating cardiac events in patients with LQT2 and LQT3 (14). Beta-blocker therapy in our population, with a prevalence of LQT1, may have influenced mortality.

Family history in LQTS, although important for establishing the diagnosis, is not helpful for risk stratification (15). Although the reasons behind the variable penetrance remain uncertain, it is becoming clear that genotype-positive relatives may have disparate clinical outcomes. Treatment of patients in the absence of symptoms may in some patients reduce the risk of symptom development while committing others to a lifetime of unnecessary therapy.

Clinical practice patterns for the management of patients with LQTS are diverse and in constant evolution. Although this was a retrospective study, there was remarkable uniformity among participating centers concerning the indications for device implantation. All 3 centers recommended device implantation in patients with documented ventricular tachycardia or TdP, syncope despite beta-blocker therapy, resuscitated sudden death, or a known SCN5A mutation. It is unlikely that there will be a future prospective trial of the management of LQTS in children. Thus, this multicenter design is a template for safe clinical practice. The management patterns of the centers participating in this series seemed to strike a reasonable balance between adverse effects of the various therapies and an excellent overall outcome.

Study limitations. Not all patients have completed genetic testing; diagnosis was made clinically by a pediatric electrophysiologist. In these patients the DNA samples were submitted to research laboratories, with lower costs but an entirely undefined timeline for results. Our population differs somewhat from the recent reports concerning genetic diagnoses because a substantially greater number had a KCNQ1 mutation (16), possibly reflecting participation of the group in Utah and the founder effect in this population. These patients are the most sensitive to beta-blocker therapy, and this may have decreased overall mortality. Additionally, a cluster of device recalls and advisories occurred during the period under study, increasing the rate of device re-intervention in a way that may not be maintained in future years, but underscoring the concern that this therapy is not without unexpected risk. The small number of deaths in this cohort weakens any comparison of mortality between patient subgroups.

Conclusions

Long QT syndrome is increasingly recognized in the absence of symptoms as family members are screened by ECG and genetic testing. Evaluation of the asymptomatic or minimally symptomatic but treated population offers an evolving understanding of this disease in the young. Past
evaluations of highly symptomatic patients, often the probands, yielded a more worrisome picture of this disease. In the era of genetic testing and device implantation, overall mortality is low in young patients with LQTS with treatment. Clinical practice patterns by 5 pediatric electrophysiologists at 3 separate institutions still regard an SCN5A mutation as a cohort that warrants ICD implantation irrespective of symptoms. Conversely, the genetic confirmation of a KCNQ1 mutation is reassuring. Patients in this group have a low mortality and are unlikely to need ICD implantation as long as there is compliance with necessary restrictions and beta-blocker therapy.

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REFERENCES