The long QT syndrome: a prospective international study

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ABSTRACT During the past 4 years 196 patients with the idiopathic long QT syndrome were enrolled in a prospective international study conducted to obtain a better understanding of the clinical course of this unusual repolarization disorder. The mean patient age was 24 years, 64% were female, and 88% had family members with QT prolongation. During an average follow-up of 26 months per patient, four patients died suddenly (1.3% per year) and 27 patients had one or more syncopal episodes (8.6% per year). Multivariate analysis identified congenital deafness, history of syncope, female gender, and a documented episode of torsades de pointes or ventricular fibrillation as independent risk factors for postenrollment syncope or sudden death. Two types of treatment (left stellate ganglionectomy and \( \beta \)-blocker therapy) were associated with a significant reduction in the occurrence of cardiac events during follow-up.


The long QT syndrome (LQTS) is an infrequently occurring idiopathic disorder in which affected individuals have an unusual electrocardiographic repolarization abnormality and a propensity to syncope and fatal ventricular tachyarrhythmias.\(^1\)\(^2\)\(^3\) The pathognomonic electrocardiographic finding is an abnormal lengthening of the QT interval with asymmetric or notched T waves. In a majority of patients with LQTS there is a familial pattern of occurrence suggesting autosomal dominant inheritance.\(^4\)\(^5\) A cardioauditory variant of this disorder is associated with congenital deafness and autosomal recessive inheritance.\(^6\)\(^7\) LQTS is a puzzling condition that predominantly affects young people with structurally normal hearts. The electrical instability and malignant ventricular arrhythmias, including torsades de pointes, are clearly related to the QT prolongation. Current evidence suggests that the life-threatening arrhythmias may be triggered or precipitated by centrally mediated discharge of the left-sided sympathetic nerves.\(^8\) Therapy with \( \beta \)-blocking drugs and/or left cervicothoracic sympathetic ganglionectomy* is frequently used in the treatment of patients with this disorder.\(^1\)\(^2\)\(^8\)\(^9\)

To obtain a better understanding of the natural history of this disease, its clinical features, and the long-term efficacy of different therapeutic approaches, a world-wide prospective study was established in 1979.\(^10\) The findings from this registry and the prospective follow-up of the first 196 patients with LQTS enrolled are the subject of this report.

Methods

The registry. A prospective LQTS study was initiated in 1979. Patients with suspected LQTS were screened for enrollment through contact with one of the three principal investigators (A. J. M., P. J. S., or R. S. C.). Information was recorded on prospectively designed forms on which were recorded demographic, electrocardiographic, historical, family history, laboratory, and therapeutic data. Electrocardiograms were obtained from all patients, and the QT interval was measured in leads II and V\(_1\). The observed QT interval was corrected for the heart rate according to Bazett’s formula.\(^11\) Patients qualified for enrollment in the registry if the corrected QT interval (QT\(_C\)) in either lead II or V\(_1\) was (1) greater than 0.44 sec or (2) equal to or greater than 0.40 sec and the patient had unexplained syncope or was a member of a family in which at least one blood relative had a QT\(_C\) of greater than 0.44 sec. Patients receiving medication known to prolong the QT interval were excluded from enrollment. The study data were maintained in a Statistical

*This term is simplified throughout the text to left stellate ganglionectomy. However, it should be emphasized that effective left-sided cardiac sympathectomy requires removal of the stellate and the first four to five thoracic sympathetic ganglia.
Analysis System (SAS) archival file on an IBM 3032 computer.

**Population.** As of September 1, 1983, 196 patients were enrolled in the LQTS study. Thirty-eight percent of the patients were identified as having the disease during clinical evaluation of unexplained syncope, 44% were identified when family members were examined, and 18% were diagnosed in a variety of other ways, including when unexpected QT prolongation was noted on a routine examination. The registered population contained 187 patients with QTc intervals greater than 0.44 sec and nine patients with QTc intervals that ranged from 0.40 to 0.44 sec.

**Follow-up.** For each patient enrolled in the study we attempted yearly follow-up with clinical visits or phone calls to evaluate the patient’s clinical course. The number of syncopal events and the dates and causes of any deaths during follow-up were recorded. Follow-up information was obtained for 146 patients (75%); in the remaining 50 patients only enrollment information was available.

**Statistical analyses.** Univariate analyses were performed with a Yates' corrected chi-square test. The multivariate contribution of selected clinical variables to the occurrence of syncope or sudden cardiac death (events) after enrollment was modeled as a Poisson process. This model assumes a constant hazard rate over time and permits the inclusion of multiple events (more than one episode of syncope per patient) in the analysis. The model uses the total number of events during the follow-up exposure time without taking into account the time when each event occurred. All but two of the patients in whom follow-up information was obtained had less than four syncopal events. One patient had nine and a second patient had 18 syncopal events during follow-up. Because of the undue weight that data from these two patients could contribute to the analysis, the number of events in these two patients was recoded as four, where the value four represents four or more events during postenrollment follow-up. For all other patients we used the actual number of recorded events. Data from patients with missing follow-ups were censored from their last contact date. It should be noted that the Poisson analysis adjusts for risk factor differences in the selected patient groups so that the independent contribution of each of the risk or therapeutic factors to the outcome event can be evaluated.

**Results**

**Population characteristics.** The pertinent clinical characteristics of the 196 patients with LQTS who were enrolled in the study are presented in table 1. The average age of the population was 24 years and there were almost twice as many women as men. Mitral valve prolapse was present in 16 patients (9%), and all were over 21 years old. Congenital deafness was present in 11 patients (6%), and all had one or more syncopal episodes before age 10. Twenty-one percent of the population had a history of tachycardia or ventricular fibrillation before enrollment. Eighty-eight percent of the enrolled patients had family members with QT prolongation. A majority of the patients were being treated with β-blocking drugs at the time of registration, and 16 patients (8%) had already undergone left stellate ganglionectomy for refractory ventricular arrhythmias.

A majority of the patients with LQTS (57%) had a history of syncope before enrollment, and many had experienced multiple episodes. Among those with a history of syncope, 58% had at least one syncopal spell that was associated with intense emotions (anger or fright), 45% had spells associated with vigorous activity, and 9% had syncope associated with loud noises.

The patients with (n = 146) and without (n = 50) follow-up data were comparable, and there were no significant differences between the two subgroups (p > .05) with respect to any of the baseline characteristics listed in table 1.

**Follow-up: univariate analyses.** In the 146 patients in whom follow-up information was available, the duration of follow-up ranged from 15 days to 48 months (average 26 months per patient). Significant follow-up cardiac events were defined as syncope or sudden cardiac death. Twenty-seven patients had one or more syncopal events (8.6% per year) and four patients died suddenly during follow-up (1.3% per year). The variables that were significantly associated with postenrollment cardiac events are listed in table 2. Of the seven risk variables identified by univariate analysis, two
were related to meaningful prior cardiac events (syncope and torsades de pointes/ventricular fibrillation), three to various types of ventricular premature beats documented by electrocardiographic Holter recording in the past, one to the duration of the QT, interval on the qualifying tracing, and one to the presence of congenital deafness.

The most significant univariate risk variable was a history of syncope. Among patients with prior blackout spells (n = 77), 34% developed significant cardiac events during follow-up compared with 7% in patients without syncope before enrollment (n = 67) (chi square = 13.2, p < .01).

**Follow-up: multivariate analysis.** Seven clinically meaningful risk variables (table 2) plus two therapy variables (β-blocker treatment at enrollment and left stellate ganglionectomy before enrollment) were entered into the Poisson model to identify the independent contribution that each factor made to follow-up cardiac events (49 recoded syncope episodes plus four cardiac deaths). The individual contributions of the risk factors to the outcome events are presented in terms of relative risk—i.e., the ratio of the risk of having a cardiac event during follow-up for patients with the factor present to the risk for patients with the factor absent. Six factors made significant independent contributions to the model (table 3). Four factors (congenital deafness, history of syncope, female gender, and the prior occurrence of torsades de pointes or ventricular fibrillation) were each associated with a significantly increased likelihood (p < .05) of syncope/sudden death. Two treatment factors (left stellate ganglionectomy and β-blocker therapy) had significant beneficial effects on outcome, i.e., they were associated with a reduction in the occurrence of syncope/death (table 3). The relative risks presented in table 3 permit quantitation of the joint risk when two or more factors coexist. The combined risk is simply the product of the relative risks of the coexisting factors.

It should be emphasized that the Poisson analysis adjusts for baseline risk factor differences in the treated (left stellate ganglionectomy and β-blockade) and non-treated patients. Thus, the observed reduction in the risk of syncope/sudden death with stelllectomy and β-blockade represents a beneficial effect independent of risk factor differences that may have existed in these treated patients.

**Discussion**

This prospective international study of almost 200 patients with LQTS, with follow-up information on three-quarters of the population, provides useful clinical information about this infrequently occurring yet life-threatening disorder. The findings from this study enhance our understanding of this syndrome, which heretofore was based on limited observations and retrospective reviews of reported cases in literature. In brief, this is an heritable electrical disorder of the heart that predominantly affects young women and is associated with a propensity to syncope and sudden death. Such events are frequently precipitated by intense emotions, vigorous physical activity, or an auditory startle stimulus.

The duration of the electrocardiographic QT interval in defining LQTS is not settled. It is frequently difficult to identify a sharp termination of the T wave to precisely quantitate the QT interval. The technique of correcting the observed QT interval for heart rate with

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**TABLE 2**

Univariate factors associated with syncope or death during follow-up

<table>
<thead>
<tr>
<th>Factors</th>
<th>Odds ratio</th>
<th>Chi square</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPB pairs</td>
<td>7.6</td>
<td>11.0</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td>7.1</td>
<td>11.0</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>History of syncope</td>
<td>6.3</td>
<td>13.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>VPB multiform</td>
<td>3.6</td>
<td>6.0</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>TDP or VF</td>
<td>3.6</td>
<td>5.1</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Any VPB</td>
<td>3.2</td>
<td>2.6</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>QTc &gt;0.46</td>
<td>3.2</td>
<td>4.3</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

VPB = ventricular premature beats that were documented by electrocardiogram or Holter recording at some time before enrollment; TDP = torsades de pointes; VF = ventricular fibrillation.

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**TABLE 3**

Multivariate factors associated with syncope/death during follow-up (Poisson model)

<table>
<thead>
<tr>
<th></th>
<th>Relative risk</th>
<th>Confidence interval (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital deafness</td>
<td>9.9</td>
<td>3.8, 26.0</td>
</tr>
<tr>
<td>History of syncope</td>
<td>4.5</td>
<td>1.9, 10.8</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.2</td>
<td>1.0, 4.8</td>
</tr>
<tr>
<td>History of torsades de pointes or ventricular fibrillation</td>
<td>2.1</td>
<td>1.0, 4.3</td>
</tr>
<tr>
<td>Therapeutic factors (beneficial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left stellate ganglionectomy</td>
<td>0.25</td>
<td>0.09, 0.65</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>0.41</td>
<td>0.21, 0.81</td>
</tr>
</tbody>
</table>

aRatio of the risk of having a cardiac event (syncope or cardiac death) during follow-up for patients with the factor present to the risk for patients with the factor absent. A relative risk less than one indicates a beneficial effect with values closer to zero indicating more marked efficacy. When a patient has two or more factors, the combined risk is simply the product of the relative risks of the coexisting factors.
use of the Bazett or Ashman formula and the traditional definition of QTc prolongation (QTc > 0.44 sec) based on these methods have come under criticism. Before we initiated this registry, we too used QTc greater than 0.44 sec as the criterion for diagnosing LQTS. However, we have observed several patients with the familial syndrome, syncope, and documented torsades de pointes in whom the QTc was in the range of 0.40 to 0.44 sec. Thus, we feel a less stringent QTc criterion is appropriate (QTc ≥ 0.40 sec) in diagnosing LQTS in patients with unexplained syncope or a family history of LQTS.

In a prior retrospective review of over 200 patients with LQTS reported in the literature, the mortality rate was roughly 5% per year during an estimated average follow-up of 5 years. In the present prospective registry the mortality rate was 1.3% per year — a value that is still remarkably high when it is realized that the average age of our population was 24 years. We believe that this lower mortality rate more accurately reflects the current risk associated with LQTS. The previously derived figure of 5% per year probably resulted from the inclusion of a large number of untreated patients and the retrospective selection bias associated with the use of unusual case studies reported in the literature.

Congenital deafness, which was present in only 6% of our population, was the most potent risk factor (relative risk 9.9). In addition to telling us something about a possible neural mechanism, it also explains why this disorder, as originally described, was first recognized in children with congenital deafness — the Jervell Lange-Nielsen syndrome.

It had previously been thought that the mortality risk among patients with LQTS was a function of the length of the QTc interval, with longer QTc durations being associated with increased risk. We dichotomized QTc at 0.46 sec to evaluate this question. In the univariate analyses, QTc greater than 0.46 sec was the weakest of the seven variables associated with syncope or death during follow-up (table 2). In the multivariate Poisson analysis, QTc greater than 0.46 sec did not enter the model as a significant independent risk factor. These findings suggest that whatever risk is associated with a QTc of greater than 0.46 sec is included within that of the four selected factors.

Therapy with β-blocking agents and/or left stellectomy has evolved as the preferred treatment for this disorder. Part of the rationale for initiating this study was to evaluate the currently used therapy over time. The Poisson analysis indicates that β-blockade and left stellectomy are associated with a reduced risk of syncope and death over a 2 year follow-up. Furthermore, combined therapy with these two treatments has an additive benefit in reducing the likelihood of an unfavorable outcome. These therapeutic findings require some qualification since the study was not a randomized, double-blind, placebo-controlled, interventional trial. Rather, it was a retrospective analysis of prospectively accumulated data in which statistical techniques were used to adjust for risk differences between treated and nontreated patients so that the independent effect of treatment on outcome could be evaluated. Each patient’s own physician was responsible for the decision as to whether to initiate β-blocker or stellectomy therapy. It is likely that the physicians selected higher risk patients for aggressive therapy. If this was the case, and if the four selected risk factors did not entirely identify the LQTS risk potential, then the quantitated beneficial effect of the antiadrenergic therapy was underestimated. On the other hand, if the physicians selected low-risk patients for therapy, and this seems unlikely, then the therapeutic benefit of β-blockade and stellectomy was overestimated. Only a prospective interventional trial can properly resolve these potential sources of error and bias.

On the basis of results of this study and our ongoing clinical experience, we would make the following therapeutic recommendations. Patients with LQTS and factors that carry high risk such as congenital deafness, history of syncope, female gender, or documented malignant arrhythmias should be prophylactically treated with β-blockers in the maximum dose tolerated. Left stellate ganglioneectomy is indicated in patients with recurrent life-threatening arrhythmic episodes refractory to β-blockade. We also recommend β-blocker treatment for patients with LQTS without the aforementioned risk factors but with a positive family history of sudden cardiac death since we have observed several untreated families in which sudden death has occurred in more than one member. At this time we do not recommend prophylactic antiadrenergic therapy in low-risk patients with LQTS and benign ventricular irritability or mitral valve prolapse.

We thank the patients and their attending physicians for participating in this study and the European Society of Cardiology for fostering the knowledge of this prospective program throughout Europe. We appreciate the useful statistical advice of Dr. Terry Thereau, the involvement of Ms. Nancy O’Daniels in patient follow-up, and the secretarial assistance of Mrs. Alice Gordon and Mrs. Nancy Kellogg.

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A J Moss, P J Schwartz, R S Crampton, E Locati and E Carleen

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