The Long QT Syndrome in Children
An International Study of 287 Patients

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Background. The Pediatric Electrophysiology Society studied children with the long QT syndrome (LQTS) to describe the features of LQTS in patients less than 21 years old, define potential “low-risk” and “high-risk” subpopulations, and determine optimal treatment.

Methods and Results. Patients less than 21 years old were included if either QTc was more than 0.44; they had unexplained syncope, seizures, or cardiac arrest preceded by emotion or exercise; or family history of LQTS. We found 287 patients from 26 centers in seven countries. Mean±SD age at presentation was 6.8±5.6; 9% presented with cardiac arrest, 26% with syncope, and 10% with seizures. Of those with symptoms, 67% had symptoms related to exercise. Family history was positive for long QT interval in 39% and for sudden death in 31%. Hearing loss was present in 4.5%. A normal QTc was present in 6%, and QTc of more than 0.60 was in 13%. Atrioventricular block occurred in 5%, but 13 of 15 patients had second-degree atrioventricular block (2:1), and only two of 287 had complete atrioventricular block. Ventricular arrhythmias were found on 16% of initial routine ECGs: 4% uniform premature ventricular contractions, 5% multifocal premature ventricular contractions, 1% monomorphic ventricular tachycardia, and 6% torsade de points. Overall, treatment was effective for symptoms in 76% and for ventricular arrhythmias in 60%. There was no difference between propranolol and other β-blockers in effective treatment. Left stellectomy was performed in nine patients, and defibrillators were implanted in four; no sudden death occurred in these 13 patients. In follow-up (duration, 5.0±4 years; age, 10.9±2.6 years), 5% had cardiac arrest, 4% had syncope, and 1% had seizures. The two multivariate predictors of symptoms at follow-up were symptoms at presentation and propranolol failure. Sudden death occurred in 8%; multivariate predictors of sudden death were length of QTc at presentation of more than 0.60 and medication noncompliance.

Conclusions. The appearance of 2:1 atrioventricular block, multifocal premature ventricular contractions, and torsade de points are relatively more common in children with LQTS than other children and should raise the index of suspicion for LQTS. Because 9% of patients presented with cardiac arrest and no preceding symptoms, perhaps prophylactic treatment in asymptomatic children is indicated. Asymptomatic patients with normal QTc, and positive family history may be a low-risk group. Patients with QTc of more than 0.60 are at particularly high risk for sudden death, and if treatment is not effective, consideration should be given to cardiac sympathetic denervation, pacemaker implantation, and perhaps implantation of a defibrillator. (Circulation 1993;87:1866–1872)

Key Words • pediatrics • electrophysiology • long QT syndrome • sudden death • arrhythmias

Diopathic long QT syndrome is a rare disorder that may lead to syncope, seizures, and sudden death.1–3 Unlike most congenital diseases, the long QT syndrome has received more attention in adults than in children.4–9 Because most centers have relatively few cases, the Pediatric Electrophysiology Society undertook this study to gather a large number of children with the purposes of describing the features of the long QT syndrome in patients less than 21 years old, defining potential “low-risk” and “high-risk” subpopulations of children with the long QT syndrome, and determining the optimal forms of treatment.

Methods
The members of the Pediatric Electrophysiology Society (all pediatric cardiologists) were asked to complete a standardized data form for each patient with the diagnosis of the idiopathic long QT syndrome. This diagnosis was based on 1) the presence of a prolonged QT interval (corrected QT [QTc] by the method of Bazett10 of more than 0.44 seconds) and the absence of any other underlying cause such as prematurity, electrolyte disturbance, or central nervous system abnormality; or 2) both a) unexplained syncope, seizure, or cardiac arrest associated with typical inciting events such as exercise or emotion and b) family history of the long QT syndrome. The entry criteria were intentionally wide, according to the criteria of Schwartz,5 to include

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as many individuals as possible initially. The patients without long QT but with other reasons for inclusion were analyzed separately as well as part of the entire group. This was a retrospective analysis of all patients who met any of the above criteria, so the patient did not have to be alive at the time of data collection. The data form sought information on age at presentation, associated findings, symptoms, family history, ECG variables (routine ECG, Holter, and treadmill), electrophysiological testing, treatment, and follow-up. The criteria for treatment effectiveness were generally similar among the institutions: treatment with pharmacological or nonpharmacological therapy was considered “effective” for symptoms if there were no symptoms within 1 year of follow-up if the patient had been followed that long or between the time of presentation and follow-up if the patient had not been followed for 1 year. Patients receiving antiarrhythmic drugs were also evaluated by Holter; treatment was considered effective for antiarrhythmic drugs if there were no ventricular arrhythmias (less than 10 uniform premature ventricular contractions per hour). A patient was judged by the physician as “noncompliant” based on either subjective questioning or objective low blood levels of drugs. The QT interval recorded was the longest found on a 12-lead ECG. The lead in which that QT interval was found was also noted. The QT interval was corrected by the method of Bazett. Patients with bundle branch block were excluded.

This patient population is different from that reported by Moss et al involving the prospective registry of long QT syndrome patients. In the Moss registry, the patients were mostly adults, with a mean age at first contact of 21 years. The patient population in the present study had a mean age at first contact of 7 years. Because the data collection in the present study involved only patient initials, it was not possible to determine directly how many of the patients reported by Moss et al are included in the present study.

Continuous variables were compared by nonpaired t test or Fisher’s exact test for small sample sizes and also were categorized for χ² analysis. Univariate associations were assessed by contingency table analysis. In our attempt to determine which independent variables predicted the dependent variables of persistent symptoms or sudden death, the independent variables were identified by contingency table analysis, and these variables then were entered into a stepwise logistic regression. Statistical significance was inferred if p<0.05.

Results

Centers Contributing Patients
Forty-five centers in seven countries contributed 287 patients to the study. The names of the centers are shown in Table 1.

| Table 1. Centers Participating in Pediatric Electrophysiology Society Study |
|-------------------------------|----------------|
| Baylor College of Medicine, Houston, Tex. | University of Gotteborg, Sweden |
| Children’s Hospital of Philadelphia | University of Groningen, The Netherlands |
| Children’s Hospital of Phoenix | University of Hannover, Germany |
| Cook Children’s Hospital, Fort Worth | University of Miami, Miami, Fl. |
| Hospital Necker-Enfants-Malades, Paris | University of Michigan, Ann Arbor |
| Hospital Sainte-Justine, Montreal | University of Minnesota, Minneapolis |
| Hospital for Sick Children, Toronto | University of Nancy, France |
| IWK Hospital, Halifax, Nova Scotia | University of Nebraska, Omaha |
| Medical University of South Carolina | University of Newcastle, England |
| Mercy Hospital, Kansas City | University of Oregon, Portland |
| State University of New York, Syracuse | University of Pittsburgh, Pa. |
| University of California, San Francisco | Wayne State University, Detroit, Mich. |

Age at Presentation
The age at presentation ranged from in utero (presenting with bradycardia) to 21 years of age (mean±SD, 6.8±5.6); 20% presented at less than 1 month of age, and 36% presented between the ages of 9 and 15 years. The age at presentation was related to sudden death: 16% of those who presented at less than 1 month of age had sudden death compared with 7% of those presenting at an older age (p<0.05).

Symptoms at Presentation
Of the 287 patients, 61% were symptomatic at presentation. Forty-five percent had “serious” symptoms: 9% of all patients presented with a cardiac arrest, 26% with syncope, and 10% with seizures. Six percent presented with the less severe symptoms of presyncope or palpitations. Other forms of symptomatic presentation occurred in 10%; only one patient presented as a result of a near-drowning episode. Among the 175 patients who presented with symptoms, 67% had symptoms related to exercise, an additional 18% were recorded to have symptoms during exercise and with emotion, 7% with emotion alone, 3% with loud noise and exercise, and 2% with anesthesia, and 3% were classified as other. Symptoms at presentation were related to ventricular arrhythmias on routine ECG (12% of the symptomatic patients had ventricular arrhythmias compared with 4% of those without symptoms, p<0.01) and longer QT interval at presentation (85% of those with symptoms had QT, 0.48 or more compared with 63% of those without symptoms, p<0.001). Fewer patients who had symptoms at presentation had a positive family history (the family history was positive in 53% of those with symptoms and 65% of those without symptoms, p<0.05).

Sex and Family History
Fifty-one percent were male, and 49% were female. The family history was positive in 60%. Of all 287
patients, the family history was positive for sudden death in 31%, syncope in 6%, and seizures in 2%. A family history of a prolonged QT interval was present in 39% of the patients (64% of those with a positive family history for a prolonged QT interval also had symptoms, whereas 36% had no symptoms). Because 89% of the patients with a positive family history had been treated and because treatment affected symptoms at follow-up and sudden death, it is difficult to assess family history as an independent risk factor.

Despite an equal distribution of males and females in the index patients as well as their brothers and sisters, there was a statistically significant \( p<0.01 \) female predominance in other relatives: 32% had a positive family history for a mother (compared with 8% for a father), 15% for an aunt (compared with 10% for an uncle), and 8% for a grandmother (compared with 4% for a grandfather). The overall ratio of female to male relatives was 1.55:1.

**Associated Findings**

Hearing loss was present in 4.5% of all the patients. Of the 12 patients, nine were from Europe and three were from the United States; this represented 8.7% of the foreign patients and 1.6% of the US patients \( p<0.025 \). Fifty percent of the deaf patients had a negative family history, 25% had a family history for both deafness and long QT, and 25% had a family history for only long QT.

Congenital heart disease was found in 12% of the patients. The types of congenital heart disease were similar in prevalence to those in children without the long QT syndrome. Noncardiac congenital disease was found in an additional 5% of the patients.

**QT Interval at Presentation**

The longest QT interval was found in lead II in 82% of the patients; \( V_1 \) was the longest lead in 6%, \( V_2 \) in 5%, and \( V_1 \) in 2%. The distribution of QTc is shown in Figure 1. A normal QT (0.44 second or less) was found in 6% of those diagnosed with the long QT syndrome; 27% had a corrected QT interval of 0.55 or more, and 13% had a corrected QT interval of 0.60 or more. A QTc at presentation of more than 0.55 was related to serious symptoms at presentation (59% of those with longer QT, had symptoms compared with 36% of those with a shorter QT, \( p<0.001 \)); younger age at presentation (61% of those with a longer QT, were under 1 month old at presentation compared with 13% of those with a shorter QT, \( p<0.001 \)), bradycardia on routine ECG (67% of those with the longer QT, had bradycardia compared with 13% of those with a shorter QT, \( p<0.001 \)), and ventricular arrhythmias on routine ECG (23% of those with a longer QT, had ventricular arrhythmias compared with 7% of those with a shorter QT, \( p<0.01 \)).

**ECG and Electrophysiological Variables**

Bradycardia was most often due to sinus bradycardia or junctional escape rhythm; 5% of the patient group had atrioventricular block. The majority (13 of 15) had second-degree atrioventricular block (most often 2:1) with P waves falling on T waves; only two of 287 patients had complete atrioventricular block. Of the 156 patients who had a Holter, 19% had a minimum heart rate that was below the normal for age, and 36% of the 103 patients who had an exercise test had a maximum heart rate lower than the normal for age. Because seven of the patients with atrioventricular block had pacemakers implanted, it is difficult to assess the presence of atrioventricular block as an independent risk factor.

Ventricular arrhythmias were found on 16% of initial routine electrocardiograms: 4% uniform premature ventricular contractions, 5% monomorphic ventricular tachycardia, 6% torsade de pointes. Ventricular arrhythmias were found in 41% of the 156 patients who had a Holter (including 6% with nonsustained monomorphic ventricular tachycardia) and 30% of the 103 patients who had an exercise test (including 3% nonsustained monomorphic ventricular tachycardia, 9% nonsustained torsade de pointes, and 1% sustained monomorphic ventricular tachycardia). The patient with sustained monomorphic ventricular tachycardia was the only one to have syncope during an exercise test.

At electrophysiology study, 74% of the 60 patients had no ventricular arrhythmia. Of the remainder, 2% had spontaneous torsade de pointes, 12% polymorphic ventricular tachycardia in response to ventricular extrastimulus testing, 7% nonsustained monomorphic ventricular tachycardia with extrastimulus testing, and 5% torsade de pointes during catecholamine infusion without ventricular extrastimuli.

**Treatment**

Pharmacological or nonpharmacological treatment was given to 82% of the patients. Treatment thought to be "effective" for ventricular arrhythmias and symptoms is shown in Figures 2 and 3. In follow-up, 51% of the patients were receiving propranolol (approximately two thirds with an additional drug), 27% other \( \beta \)-blocker (with three fourths receiving an additional drug), 5% phenytoin, and 3% mexiletine; 2% had undergone left stellactomy, 15% had had pacemaker implantation, and 1% had a defibrillator implanted. All patients who had nonpharmacological therapy also received pharmacological therapy. Phenytoin was statistically less effective than propranolol or other \( \beta \)-blockers in terms of effective treatment of either symptoms and ventricular arrhythmias, whereas mexiletine was less effective than propranolol or other \( \beta \)-blockers only in terms of ventricular arrhythmias. Sudden death occurred in 9% of the pa-
patients receiving propranolol, 5% of those who were receiving other β-blockers, and 16% of those who had had a pacemaker implanted (46% of those with pacemakers had propranolol failure); 17% of those who had sudden death were not being treated. There were no sudden deaths in any of the other treatment groups.

In patients treated with drugs, 39 received more than one drug, thus enabling a calculation of drug concordance and discordance. As shown in Table 2, 34 of 39 patients had concordance for drug therapy, meaning that in the same person, drugs were either both effective or both ineffective.

"Effective" treatment with any mode of therapy could not be predicted on the basis of any other variable. Therefore, age, sex, QT interval, type of symptoms, and type of ventricular arrhythmia were not predictors for effectiveness of treatment.

The 50 patients who received no treatment are potentially informative because these are the ones who may represent the "natural history" of the syndrome. However, they do not because they clearly had milder forms of the disease. Compared with the patients who did receive treatment, those who did not receive treatment had less serious symptoms at presentation (12% had serious symptoms compared with 55%, p<0.001), less bradycardia on routine ECG (6% compared with 24%, p<0.01), shorter QT at presentation of less than 0.46 (56% compared with 17%), and higher positive family history (62% versus 35%, p<0.001). Of the 50 patients who were not treated, two died suddenly; both had a positive family history.

Follow-up

Follow-up ranged from 1 day to 26 years (mean, 5.0±4.6 years). The majority of patients had between 1 and 5 years of follow-up; however, 35% of the patients had more than 5 years of follow-up. The mean age at follow-up was 10.9±6.3 years. The age at follow-up was significantly greater (p<0.025) for the survivors (11.7±0.4 [SEM] compared with those who died (age at death, 9.2±1.5 years). In follow-up, the QT interval did not change significantly. However, of those who had a QTc at presentation of less than 0.50, 15% had a QTc of more than 0.50 at follow-up. Of those who had a QTc at presentation of more than 0.50, 32% had a QTc of less than 0.50 at follow-up.

Within 1 year of the most recent follow-up, 16% had symptoms: 5% with cardiac arrest with resuscitation, 4% syncope, 1% seizure, 4% presyncope, and 2% palpitations. Sudden death during the 5 years of follow-up occurred in 8% of the patients. Approximately two thirds of the patients who had sudden death were asymptomatic in the year before their sudden death.

Long QT Syndrome Without Long QT Interval

Of the 287 patients, 17 (6%) had a QTc of less than 0.44 at presentation; six were identified as having the syndrome because of typical "serious" symptoms (four of six also had a positive family history), nine were identified because of a positive family history only, and two were identified because of a long QTc on Holter in the absence of symptoms with a positive family history. In follow-up, two of six patients with serious symptoms continued to have serious symptoms despite treatment. Of the nine patients with a positive family history only, seven were treated, and none had symptoms at follow-up. Two of nine were not treated, and one of these two had late sudden death. Of the two patients who presented with QTc prolongation on Holter only, neither was treated, and there were no late symptoms on follow-up. Among all 17 patients with normal QTc at presentation, in three, the QTc was found to be more than 0.44 at follow-up; each of these was 0.46 or more. All three of these patients had serious symptoms or sudden death at follow-up, whereas none of the patients in whom the QTc remained at less than 0.44 had either symptoms or sudden death at follow-up.

High Risk: Serious Symptoms at Follow-up

Serious symptoms at follow-up (arrest, syncope, or seizure) were related in a univariate analysis to QTc of more than 0.60 at presentation or follow-up (38% of those with QTc of 0.60 or more had late symptoms compared with 7% of those with QTc of less than 0.60, p<0.001), bradycardia for age (17% of those with bradycardia for age had late symptoms compared with 7% of those without late bradycardia, p<0.025), and pacemaker use (22% of those with pacemakers had late symptoms compared with 7% of those without pacemakers, p<0.001). In multivariate analysis, the two statistically significant variables that predicted late serious symptoms were propranolol failure and symptoms at presentation. Of note is that in the presence of propranolol failure, pacemaker use did not significantly prevent symptoms.
Of the patients who were asymptomatic at presentation and had a positive family history and a long QT on their own ECG, 12% developed serious symptoms at follow-up.

**High Risk: Sudden Death**

On univariate analysis, a large number of variables were shown to be correlated with sudden death. However, largely due to the high intercorrelation among the variables, only two—QTc at presentation and medication noncompliance—were statistically related to sudden death on multivariate stepwise logistic regression. The data relating QTc at presentation, medication noncompliance, and probability of sudden death are shown in Figure 4. For those with extremely long QTc (0.60 or more), the probability of sudden death in patients who were compliant with their medical regimen was 27–44%, and the probability of sudden death for those who were not compliant with their medication regimen was 83–91%.

**Discussion**

**Children Compared With Adults**

The diagnostic criteria for the long QT syndrome established by Schwartz4 based on studies in adults and children include the “major” criteria of QTc of 0.44 or more, typical symptoms, positive family history, and the minor criteria of bradycardia, hearing loss, typical morphology of T waves, and T wave alternans. He proposed that to be diagnosed as having the syndrome, the patient should have either two major criteria or one major criterion and two minor criteria. Based on the present study, the criteria appear to be generally valid in our population as well. We did not examine T wave morphology due to the subjective nature of this assessment among 26 different investigators. However, we did address the other criteria. On the basis of this study, although it is not possible to establish major and minor criteria, it appears that a small percentage of children may have the long QT syndrome without the long QT interval. Therefore, it appears reasonable in the assessment of patients for the presence of the long QT syndrome to include typical symptoms and a positive family history. In addition, because 20% of the patients had bradycardia (with 5% having second-degree atrioventricular block rather than the previously reported complete atrioventricular block)12 and 12–24% of the patients had multiformal premature ventricular contractions, monomorphic ventricular tachycardia, or polymorphic ventricular tachycardia on routine ECG, Holter, or treadmill testing, the finding of these types of arrhythmias should alert the clinician to the possibility of the long QT syndrome. Because 85% of those with symptoms presented with symptoms during exercise, it also appears that when a child presents with rapid palpitations or syncope during exercise, the long QT syndrome should be suspected.

In comparison with other reported series in adults and children,5,11,13 the prevalence of congenital heart disease was high in our patients, although congenital heart disease was not statistically related to mortality in this study. This may be a selection bias due to the fact that all the investigators in this study were pediatric cardiologists. It is not known whether these factors were specifically assessed in the other studies because this factor is not mentioned.

Because the children who presented at the youngest ages were most likely to die suddenly, this finding would suggest that studies in adults are skewed in favor of those that survived. Therefore, conclusions about risk of death and requirements for treatment in children probably should be based more on studies relating specifically to this age group.

**Low Risk—High Risk**

Because the majority of patients received treatment and because treatment has been shown in other studies to be effective in preventing sudden death,13,14 it is difficult to determine the relative risk factors. There were only two patients in the entire series who had a diagnosis of the long QT syndrome made entirely on the basis of Holter monitoring; neither of these patients had symptoms, a positive family history, or a prolonged QTc on their routine ECG. It is possible that this type of patient represents a low risk for sudden death. The other candidate group for low risk are the patients with normal QT intervals at presentation, no symptoms, and only a positive family history. The inclusion of patients with a normal QT interval was first suggested by Schwartz in 1980.15 We had nine such patients. There was one sudden death in this group of nine, in one of the only two patients not treated. This would appear to argue in favor of treatment of these patients. On the
other hand, among all 17 patients with a normal initial QTc, three patients had a prolonged QTc at follow-up. All three of these patients had symptoms or cardiac arrest, whereas none of the patients whose QTc did not prolong with time had symptoms or cardiac arrest. Therefore, it could also be argued that asymptomatic children with a positive family history of the long QT syndrome who present with a normal QT interval should be followed closely for the development of prolongation of the QT interval, and if this occurred, treatment could be considered.

A large number of univariate parameters were associated with late symptoms and sudden death, including bradycardia and symptoms at presentation; the two parameters that remained significant on multivariate analysis were length of the QT interval and noncompliance. The length of the QT interval was also predictive of an increase in late syncope or sudden death in the prospective registry with a group of largely different older patients.15

Implications for Treatment

Among these children, 9% presented with a cardiac arrest. This is unlike the data in adults where the majority had syncopal episodes before a cardiac arrest.15 Analysis of the data in the present study compared with the adult studies indicates that children who die may select out a potential group of survivors into adulthood.1,2,16 At the present time, it appears that children with a QTc of more than 0.44 and a positive family history of the long QT syndrome should be treated, despite the lack of symptoms, because a cardiac arrest may be the first symptom. This conclusion can be debated from the standpoint that this will result in a large number of children being treated unnecessarily. This argument should be viewed in light of the data that in this study, 12% of such patients later developed symptoms and 4% had sudden death. As better diagnostic data are developed, this conservative recommendation is likely to be modified.

The observation from this study that both ineffective treatment and noncompliance with previously effective treatment are predictors of symptoms and sudden death could imply that effective treatment may prevent sudden death. However, because 5% of the patients who were thought to be “effectively” treated in our study had sudden death, this raises the question of whether the medicine was truly effective in certain patients or whether the criteria for “effective treatment” should be made more rigorous. We did find that among those who had sudden death, fewer patients had had Holters and treadmill tests performed at follow-up than those who did not die, perhaps suggesting that the use of these tests might be beneficial in the definition of effectiveness.

In our data, propranolol was equal to other β-blockers in providing effective treatment for symptoms and ventricular arrhythmias; there was a similar incidence of late sudden death with these two types of treatment. Within the group who received β-blockers other than propranolol, sudden death was not related to the type of other β-blocker, with no statistically significant difference between nadolol and atenolol. These data are in contrast to a previous report on a smaller number of children.17

We found that ineffective treatment, especially for symptoms, was a predictor for late symptoms and sudden death. We also found that ineffective treatment with one drug regimen probably predicted ineffective treatment with other drug regimens, and therefore, it appears that if a patient continues to have severe symptoms on one drug regimen, consideration should be given to nonpharmacological treatment such as a pacemaker or left cardiac sympathetic denervation. Recent studies have demonstrated a reduction in symptoms using either technique.18–20 Because of the large number of confounding variables, it cannot be determined, on the basis of this study, whether the addition of nonpharmacological therapy will prevent sudden death.

On the basis of our study, children with extremely long QTc (more than 0.55–0.60) are at high risk for sudden death. In this small subgroup of patients with the long QT syndrome, the occurrence of sudden death was not related to the presence of continuing symptoms or continuing ventricular arrhythmias. This implies that it may be extremely difficult to predict which of those children with extremely long QT intervals will have sudden death. Although the implantation of a defibrillator appears to be an extreme measure in a child, it may be that in this subgroup of patients with extremely long QT intervals,21 especially if they are not treated effectively or noncompliant, consideration should be given to implantation of a defibrillator to save their lives. Fortunately, this extremely high-risk group is small in number, and the majority of children with the long QT syndrome appear to have a good prognosis as long as they respond to treatment.

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