Age- and Sex-Related Differences in Clinical Manifestations in Patients With Congenital Long-QT Syndrome

Findings From the International LQTS Registry

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Background—Unexplained female predominance is observed in long-QT syndrome (LQTS), a congenital autosomal disorder with prolonged repolarization and syncope or sudden death due to ventricular tachyarrhythmias. Our objectives were to evaluate age- and sex-related differences in events among LQTS patients referred to the LQTS International Registry.

Methods and Results—Age- and sex-related occurrence of events was analyzed in 479 probands (70% females) and 1041 affected family members (QTc > 440 ms, 58% females). LQTS-gene mutations were identified in 162 patients: 69 LQT1 carriers (KVLQT1 on 11p15.5), 62 LQT2 carriers (HERG on 7q35-36), and 31 LQT3 carriers (SCN5A on 3p21-24).

Females predominated among 366 probands (71% females) and 230 symptomatic family members (62% females). Male probands were younger than females at first event (8.7 versus 14.1 years, P < 0.0001) and had higher event rates by age 15 years than females (74% versus 51%, P < 0.0001). Affected family members had similar findings. By Cox analysis adjusting for QTc duration, the hazard ratio for female probands of experiencing events by age 15 years was 0.48 (P = 0.001), and it was 1.87 (P = 0.09) by age 15 to 40 years. In female family members, the hazard ratio was 0.58 (P < 0.001) by age 15 years, and it was 3.25 (P < 0.001) by age 15 to 40 years. The event rate was higher in male than female LQT1 carriers (69% versus 32%, P = 0.001). No age-sex difference in event rate was detected in LQT2 and LQT3 carriers.

Conclusions—Among LQTS patients, the risk of cardiac events was higher in males until puberty and higher in females during adulthood. The same pattern was evident among LQT1 gene carriers. Unknown sex factors modulate QT duration and arrhythmic events, with preliminary evidence of gene-specific differences in age-sex modulation. (Circulation. 1998;97:2237-2244.)

Key Words: long-QT syndrome ■ genes ■ sex ■ syncope ■ death, sudden

An unexplained female predominance has been reported in congenital long-QT syndrome (LQTS), a disorder characterized by syncope and unexpected death due to malignant ventricular arrhythmias associated with congenital prolongation of ventricular repolarization.1-5 The original observation of female predominance among LQTS patients was made by Hashiba in 1978,6 even though this pattern was already present in the survey of 203 LQTS patients published in 1975.7 In the initial report of 186 patients enrolled in the International LQTS Registry, females were predominant and had a higher risk of events (syncope or sudden death) than did males.8 This increased female prevalence was consistently found among the growing number of patients referred to the LQTS Registry.9,10

The clinical diagnosis of LQTS is based primarily on QT interval duration.11 However, QT interval duration is per se age- and sex-dependent, even in normal subjects in whom QT duration is similar by sex during childhood, but it is shorter in adult males than females.12-14 In the absence of definite sex-specific criteria for QT duration, such differences may
induce a bias, favoring LQTS diagnosis among adult females.\textsuperscript{11,15}

The unbalanced sex distribution cannot be accounted for by genetic transmission, because the inheritance pattern is not concordant with a sex-linked disease.\textsuperscript{15,16} At least three autosomal mutant genes have already been identified,\textsuperscript{17–22} and more candidate genes are currently under evaluation.\textsuperscript{24}

The aims of this study were (1) to evaluate age and sex differences in clinical manifestations among LQTS patients and (2) to explore whether such differences were also present among patients with known LQTS gene mutations, in whom LQTS diagnosis is independent of QT interval duration.

### Methods

#### International LQTS Registry

The logistics of the International LQTS Registry have been presented in detail elsewhere.\textsuperscript{17–22} Index cases (proband) were referred to one of the participating centers: Rochester, NY; Milan, Italy; Salt Lake City, Utah; and Jerusalem, Israel. In most probands (68%), the diagnosis was made during workup of syncope or nonfatal cardiac arrest, and in the remaining cases during workup of unexpected sudden death in the family. To qualify for enrollment, probands had to have QT interval corrected for heart rate (QT\textsubscript{c}) by modified Bazett’s formula\textsuperscript{25} >440 ms in lead 2 (or another bipolar lead satisfactory for QT quantification) on resting 12-lead ECG. First- and second-degree relatives identified by pedigree analysis were also enrolled. All probands and family members gave informed consent for enrollment. Yearly follow-up contact was made with enrolled families to record symptoms and current medications. The reported database (release 6) included 479 probands and 5275 family members. At least one ECG was available for all probands and 2778 family members (53%). The first recorded ECG (baseline) was used to categorize patients. The same ECG criterion as used for proband definition (QT\textsubscript{c} >440 ms) was used to define the “affected status” among family members (n=1041, 37\% of the family members with available ECG). Syncope, nonfatal cardiac arrests, and unexplained sudden deaths before age 40 years were used as end points, whereas events after age 40 years were censored. Syncope and/or LQTS-related death was recorded in 366 probands and 572 family members. To minimize the confounding effect of beneficial therapies, this analysis was focused on first events, when almost all patients were still free of therapy.

### Patients With Genotype Analysis

Within the database used for this analysis, a total of 162 LQTS gene carriers were identified out of 333 subjects tested for LQTS gene mutations within 28 families enrolled in the LQTS registry. All patients gave informed consent for gene analysis. Gene mapping in these families has been described elsewhere.\textsuperscript{17–22} \textit{KVLQT1} mutations on chromosome 11p15.5 (LQT1) were identified in 7 families, with 69 LQT1 carriers out of 146 tested subjects; \textit{HERG} mutations on 7q35–36 (LQT2) in 16 families, with 62 LQT2 carriers out of 124 subjects; and \textit{SCN5A} mutations on 3p21–24 (LQT3) in 5 families, with 31 LQT3 carriers out of 63 subjects.

### Data Management and Statistical Analysis

Data were maintained on a relational database on a Sun Sparc-Server 470 computer. Analyses were performed with SAS version 6.09. Univariate analyses were computed by Student’s \textit{t} test, Mann-Whitney-Wilcoxon’s two-sample test, or Yates’s corrected \(\chi^2\) test, as applicable. The age-related probability of experiencing a first event with birth used as time of origin by sex was determined by Kaplan and Meier’s life-table method.\textsuperscript{26} Differences in age-related probability of events between sexes were tested by log-rank analysis; differences at specific age levels were tested by the Greenwood formula for standard errors.\textsuperscript{26} Because most probands had a cardiac event as part of their identification as probands, some time-to-first-event curves were converted to conditional form (conditioned on having an event by age 40 years, by dividing through the estimated probability of an event by age 40 years). This made curves for probands and affected family members comparable; such procedures also removed sex differences in cumulative risk at age 40 years and permitted comparisons of the shapes of the curves across ages. Equalities of resulting conditional probabilities at age 15 years were tested by use of the difference between logit transforms of the two estimated conditional probabilities compared with its standard errors.\textsuperscript{26} The contribution of sex and QT\textsubscript{c} duration (expressed by 10-ms increase) to the risk of experiencing a first cardiac event (hazard ratio) was determined by Cox regression analysis.\textsuperscript{27} Two time intervals (from birth through age 15 years and from age 15 to 40 years) were considered in the model.

### Results

#### Clinical Characteristics of Patients Referred to LQTS Registry

**Probands**

Probands had markedly prolonged repolarization, with almost half of them having QT\textsubscript{c} >500 ms. A significant female
predominance was observed among probands. However, males were younger at initial contact than females (Table 1). The enrollment ratio of male and female probands (M:F) was 1:1 up to age 15 years and decreased markedly thereafter (Figure 1). The reduced enrollment of adult males after age 15 years reflected the fact that only 8% of males, compared with 40% of females, had first cardiac events after age 15.

Among probands with a history of cardiac events (n=366), females were altogether predominant (71%), yet males were younger at first event than females (Table 2). Of note, heart rate and QTc duration were similar among male and female probands irrespective of age.

Family Members

Altogether, among 5275 family members and among 2778 family members with an available ECG, no sex preference was observed. However, females predominated among 1041 family members with QTc >440 ms (58% females, P<0.01; Table 1). As among probands, the male-to-female ratio (M:F) was 1:1 up to age 15 and decreased thereafter (Figure 1). This pattern reflected the fact that the mean QTc duration was similar in males and females until age 15 years (442±47 versus 441±44 ms, P=NS) and shortened in males but not in females after age 15 years (429±43 versus 447±43 ms, P<0.0001), despite similar heart rate decreases after puberty in both sexes.

Within the enrolled families, a history of cardiac events was recorded in 572 individuals (61% females, P<0.01). Among them, females predominated among 230 family members with QTc >440 ms (62% females, P<0.01). Even if the event rate was similar for both sexes, males were younger at first event than females, and no age-sex difference in QTc duration was observed (Table 2).

Females also predominated among the remaining 342 family members with a history of cardiac events but with no available ECG information, including 181 family members with unexplained sudden death (61% females, P=0.003). In almost half of the cases, unexplained death was the first known event. Males died at lower age than females (13 versus 20 years, P<0.0001), and sudden death occurred as first symptom more often in males than in females (32% versus

![Figure 1. Percent distribution of probands (top) and family members with QTc >440 ms (bottom) by sex and age at baseline ECG. Horizontal axis is age by 5-year increments. Within each 5-year age group, proportion of males (solid bars) and females (hatched bars) was similar until age 15 years (male:female ratio ~1:1), whereas females became predominant afterward; a similar pattern was present among probands and affected family members. Numbers above each column are actual number of patients in each age group.](http://circ.ahajournals.org/)

### TABLE 2. Clinical Characteristics of LQTS Patients With Cardiac Events and QTc >440 ms

<table>
<thead>
<tr>
<th></th>
<th>Probands</th>
<th></th>
<th>Family Members</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first cardiac event, y</td>
<td>14±10</td>
<td>8±7</td>
<td>16±9</td>
<td>9±7</td>
</tr>
<tr>
<td>First event at age &lt;15 y, n (%)</td>
<td>130 (60)</td>
<td>98 (92)</td>
<td>64 (45)</td>
<td>70 (80)</td>
</tr>
<tr>
<td>Median No. of cardiac events</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Median event rate per year*</td>
<td>0.24</td>
<td>0.27</td>
<td>0.11</td>
<td>0.16</td>
</tr>
<tr>
<td>Ventricular tachyarrhythmias†</td>
<td>150 (58)</td>
<td>41 (38)</td>
<td>24 (17)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Baseline ECG parameters</td>
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</tr>
<tr>
<td>Age at ECG, y</td>
<td>21±12</td>
<td>13±11</td>
<td>31±18</td>
<td>18±17</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71±19</td>
<td>73±22</td>
<td>NS</td>
<td>74±19</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>519±61</td>
<td>519±58</td>
<td>NS</td>
<td>500±50</td>
</tr>
<tr>
<td>QTc &gt;470 ms, n (%)</td>
<td>205 (79)</td>
<td>95 (89)</td>
<td>NS</td>
<td>74 (52)</td>
</tr>
<tr>
<td>QTc &gt;500 ms, n (%)</td>
<td>117 (45)</td>
<td>52 (49)</td>
<td>NS</td>
<td>49 (34)</td>
</tr>
</tbody>
</table>

*Plus-minus values are mean±SD; n values are absolute number of observations (see text for statistical tests applied).

†Recording of torsade de pointes and/or ventricular fibrillation.
19%, $P<0.05$), whereas most females had repetitive nonfatal cardiac events before death.

**Age- and Sex-Dependence of First Cardiac Events**

The cumulative age-related probability of experiencing a first cardiac event in probands was significantly different between males and females ($P<0.0001$) (Figure 2). The probability of first event by age 15 years was higher in males than in females among probands (74% vs 51%, $P<0.0001$) and among family members (20% vs 16%, $P<0.01$), whereas it was similar by sex by age 40 years in both groups.

When sex-specific age distributions at first cardiac event were conditioned on the estimated occurrence of an event by age 40 years (and restricted to individuals with QTc $>440$ ms), thereby correcting for identification distinctions between probands and family members, shapes of the age distributions were significantly different by sex but almost identical between probands and family members (Figure 3). The conditional probability of having already experienced a first cardiac event by age 15 years was higher in males than in females both among probands (81% vs 56%, $P<0.0001$) and among affected family members (77% vs 47%, $P<0.0001$).

A similar pattern was present also among symptomatic family members without ECG information, including 181 family members with unexplained sudden death, in whom the death rate by age 15 years was twice as high in males as in females (57% vs 29%, $P<0.0001$).

**Predictors of First Cardiac Events**

The Cox proportional hazard regression model was used to determine the effect of sex on first cardiac events after adjustment for possible sex differences in QTc values. Among probands, males had a higher risk of first cardiac events (Table 3). When the analysis was focused on defined time periods, males had an even higher risk of events between birth and age 15 years, whereas females were at higher risk of first events between ages 15 and 40 years. Among family members, the age-related sex risk for first cardiac events was similar to that in probands, and QTc increments also made a significant contribution to the model. Such an age-dependent effect of sex on risk of first events was evident also when probands and family members with QTc $>440$ ms were combined and when all registered family members were considered, independently of their QTc duration (data not shown). Similar results were also obtained when only probands and family members with QTc $>470$ ms were considered.

Thus, among LQTS patients, the risk of first cardiac events was higher in males before age 15 years and lowered thereafter; in contrast, females remained at risk of first events in adulthood.

**LQTS Gene Carriers**

Among 162 LQTS gene carriers, no sex preference was observed (54% females, $P=NS$), with similar event incidence in males and females (41% versus 42%, $P=NS$). However, among LQT1 carriers (51% females, $P=NS$), males ($n=22$) were younger than females ($n=17$) at first event (Table 4), and the cumulative age-related probability of first event by age 15 years was higher in males than females (69% versus 32%, $P=0.04$) (Figure 4).
Female LQT2 carriers had a similar incidence of cardiac events (n=18, 45%) and a similar age-related probability of first event by age 15 years compared with female LQT1 carriers (29% versus 32%, P=NS). However, the number of male LQT2 carriers with a history of cardiac events (n=6) was too small to perform survival analysis by sex.

Among LQT3 carriers, the number of males (n=4) and females (n=2) with a history of cardiac events was also insufficient to perform survival analysis by sex. However, LQT3 male carriers had significantly lower heart rates and longer QTc intervals than LQT1 and LQT2 carriers, whereas no gene-specific differences in heart rate and QTc duration were detected among females (Table 4).

**Discussion**

The major finding of this study is the identification of sex-related differences in age at onset of events (syncope, nonfatal cardiac arrest, or unexplained sudden death) within LQTS families. In males, the risk of first cardiac events was higher in childhood and decreased after puberty; in females, in contrast, the risk of first cardiac events did not decrease in adulthood. This finding supports the original observation made by Hashiba showing the regression of LQTS phenotypic manifestations, both QTc duration and cardiac events, among affected males after puberty. Age- and sex-dependent differences in clinical manifestations are also present among patients with LQTS-gene mutations, supporting the initial observation made by Vincent et al showing sex differences in the onset and duration of symptoms among LQTS gene carriers.

**Age and Sex Differences in Clinical Manifestations**

This study provides evidence of age-dependent differences between males and females in the risk of experiencing a first cardiac event. Specifically, survival analyses show that males had earlier onset of events and higher risk of first events in childhood than females. Cox analyses, assessing the contribution of sex to the risk of cardiac events after adjustment for QTc duration, show that female sex is associated with lower incidence of events below age 15 years and higher incidence of events above age 15 years (Table 3). Such patterns were equally present among probands, affected family members, family members with unexplained sudden death, and patients with known genotype. Moreover, among LQT1 gene carriers, all first cardiac events occurred in males before age 15 years, although no explanation for this phenomenon can yet be provided.

Among patients enrolled in the LQTS registry, the referral of patients in childhood was similar by sex, consistent with other
studies including pediatric LQTS patients.29 In contrast, probands referred to the LQTS Registry in adulthood were virtually all females. The female predominance was present not only among probands but also among adult affected family members (Figure 1), suggesting that this pattern was not simply the result of a bias in proband referral. Females predominated even when a more stringent cutoff (ie, QTc >470 ms) was applied. Thus, the age-sex imbalance present among LQTS patients is not simply due to the relatively broad QTc criteria used to define the affected status in this analysis (QTc >440 ms), but it also may reflect the fact that only few males had a first cardiac event after age 15 years, whereas about half of the females had a first event after that age.

**Age-Sex Differences in QT Interval Duration**

The lower incidence of cardiac events among adult males may be due to shortening QTc duration, more prominent in males than in females after puberty. The QTc is known to be age- and sex-dependent in the normal population, with lower values in adult males.12,13 A recent study from our group showed that among patients with identified LQTS genotypes, adult males had shorter QTc duration than adult females and children.30 Thus, the same factors that affect the normal evolution of QTc duration may be active in LQTS patients as well, explaining the lower incidence of events among adult males.

Several previous studies reported a significant association between longer QTc interval duration and increased risk for cardiac events in LQTS patients, together with a higher risk of cardiac events among females.8–10 It is then possible that those patients (more often females) whose QTc did not shorten with age remained at higher risk of cardiac events later in life.

**Mechanisms Involved in Age-Sex Differences**

The mechanisms responsible for age-sex differences in QTc duration are still unknown.31,32 Sex hormones may contribute to QT interval shortening in males or to lack of shortening in females. Androgens may blunt QT interval prolongation to quinidine.33 In contrast, estrogens may modify the expression of ion channels, and specifically potassium currents, at least in rat uterus.34 Preliminary data also suggest that estradiol may have an acute dose-dependent blocking effect on Iks.35 Female LQTS patients with mutations impairing potassium channel activity may then be specifically sensitive to estrogen activity. Furthermore, adult female patients may be exposed to conditions, such as menses and pregnancy, in which hormonal changes favor QT prolongation and vulnerability to arrhythmias.31,36

The lower heart rate may also induce shorter QTc duration in males than in females with similar absolute QT interval duration both in normal subjects and in LQTS patients.12,13,31 Consistent with previous findings,10,37 we observed gene-specific differences in heart rate and QTc duration among LQTS patients (Table 4). Lower heart rate and longer QTc duration were evident among male LQT3 carriers. Such findings are still unexplained, and the number of genotyped patients is still too small to draw definitive conclusions on possible age- and sex-related gene-specific differences.

Sex differences in the QT interval–heart rate relationship may be important in LQTS patients. Lower-than-normal heart rate may be a potential risk factor in LQTS patients,38 specifically in LQT3 carriers, in whom it may facilitate further prolongation of QT interval duration and arrhythmogenesis.39 Males may have more blunted QT prolongation at a slower heart rate than females13,30; thus, they may be protected against torsade de pointes, often facilitated by bradycardia.40,41

| Clinical history                      |  |  |
|--------------------------------------|  |  |
| History of cardiac events, n (%)     | Females | Males | Females | Males | Females | Males |
| Median age at first event, y          | n=35 | n=34 | n=40 | n=22 | n=12 | n=19 |
| First event at age <15 y, n (%)      | 17 (49) | 22 (65) | 18 (45) | 6 (27) | 2 (17) | 4 (21) |
| Median No. of cardiac events         | 2 | 4 | 2 | 1 | 1 |
| Ventricular tachyarrhythmias, n (%)  | 3 (8) | 2 (6) | 10 (24) | 0 (0)* | 1 (8) | 1 (5) |

**TABLE 4. Sex Differences Among LQTS Patients With Identified Genotype**

<table>
<thead>
<tr>
<th>ECG parameters</th>
<th>LQT1 Carriers</th>
<th>LQT2 Carriers</th>
<th>LQT3 Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at ECG, y</td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Heart rate, bpm§</td>
<td>74±19</td>
<td>78±20</td>
<td>72±18</td>
</tr>
<tr>
<td>QTc interval, ms</td>
<td>504±51</td>
<td>494±45</td>
<td>514±63</td>
</tr>
<tr>
<td>QTc &gt;440 ms, n (%)</td>
<td>33 (94)</td>
<td>32 (93)</td>
<td>37 (92)</td>
</tr>
<tr>
<td>QTc &gt;470 ms, n (%)</td>
<td>15 (42)</td>
<td>11 (33)</td>
<td>16 (39)</td>
</tr>
</tbody>
</table>

P=± values are mean±SD; n values are absolute number of observations (see text for statistical tests applied).

*P<0.05 between sexes.
†P<0.001 between sexes.
‡Recording of torsade de pointes and/or ventricular fibrillation.
§P<0.05 among genotypes within males.
∥P<0.001 among genotypes within males.
Recording of torsade de pointes was more common among female than male LQTS patients, even among LQTS gene carriers, and particularly among LQT2 carriers. This finding is in agreement with the well-known female predominance observed among patients with torsade de pointes associated with acquired prolonged repolarization, regardless of the agent provoking QT prolongation.40–42 Thus, female sex may be per se predisposed to the occurrence of self-terminating torsade de pointes, whereas fatal arrhythmias and ventricular fibrillation may be prevalent among males because of unknown sex differences in the electrophysiological substrate.31,40 This may have a parallel in the unexplained increased male predominance among patients with idiopathic ventricular fibrillation.43

Clinical Implications and Limitations
Within LQTS families, males were at higher risk of first events until puberty, whereas females remained at high risk of first events in adulthood. The clinical expression of the disease was also age- and sex-dependent among LQT1 carriers, among whom males had earlier onset of cardiac events than females. The age-sex differences in clinical manifestations may contribute to the unexplained sex imbalance among patients referred to the LQTS Registry. Diagnosis of LQTS may be more likely in females, with later onset of repetitive nonfatal events, whereas LQTS may remain undetected in males, with earlier onset of fatal cardiac events. Young affected males should be considered a group at high risk of potentially serious events. However, the risk of cardiac events may decline with age in affected males, provided that their QTc shortens adequately after puberty. The present analysis, being focused on first cardiac events, does not show whether the risk of further events declines in males following QTc shortening after puberty. To explore this aspect, the occurrence of subsequent events and age-dependent changes of rate-corrected QT interval should be correlated, adjusting for the potential confounding effect of beneficial therapies.

A potential clinical implication of the present findings is that the need for treatment among LQTS patients varies with age more among males than among females, concomitantly with the individual evolution of QTc, duration. Affected females, even if still free of cardiac events, should be considered for prophylactic therapy because of the persistent risk of first events and torsade de pointes in adult life.

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References


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