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Risk of death in the long QT syndrome when a sibling has died

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Abstract

BACKGROUND—Sudden death of a sibling is thought to be associated with greater risk of death in long QT syndrome (LQTS). However, there is no evidence of such an association.

OBJECTIVE—To test the hypothesis that sudden death of a sibling is a risk factor for death or aborted cardiac arrest (ACA) in patients with LQTS.

METHODS—We examined all probands and first- and second-degree relatives in the International Long QT Registry from birth to age 40 years with QTc ≥ 0.45 s. Covariates included sibling death, QTc, gender by age, syncope, and implantable cardioverter-defibrillator (ICD) and beta-blocker treatment. Endpoints were 1) severe events (ACA, LQTS-related death) and 2) any cardiac event (syncope, ACA, or LQTS-related death).

RESULTS—Of 1915 subjects, 270 had a sibling who died. There were 213 severe events and 829 total cardiac events. More subjects with history of sibling death received beta-blocker therapy. Sibling death was not significantly associated with risk of ACA or LQTS-related death, but was associated with increased risk of syncope. QTc ≥ 0.53 s (hazard ratio 2.5, $p < 0.01$), history of syncope (hazard ratio 6.1, $p < 0.01$), and gender were strongly associated with risk of ACA or LQTS-related death.

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CONCLUSIONS—Sudden death of a sibling prompted more aggressive treatment but did not predict risk of death or ACA, whereas QTc ≥ 0.53 s, gender, and syncope predicted this risk. All subjects should receive appropriate beta-blocker therapy. The decision to implant an ICD should be based on an individual's own risk characteristics (QTc, gender, and history of syncope).

Keywords

long QT syndrome; sudden cardiac death; torsades; syncope; risk stratification

Congenital long QT syndrome (LQTS) is recognized as a cause of syncope and sudden cardiac death (SCD) in children and young adults.¹ Although the past several years have seen considerable advances in our understanding of the genetic causes of LQTS,^{2–4} clinicians still confront the need to stratify risk of SCD in individual patients in an effort to determine appropriate therapy. LQTS patients judged to be at significant risk benefit from beta-blocker therapy⁵ and from left cardiac sympathetic denervation.⁶ Patients at highest risk benefit from an implantable cardioverter-defibrillator (ICD).^{7–9} Indicators of high risk include a personal history of aborted SCD or syncope, excessive QT prolongation, age and gender,^{8,10–13} and genotype.¹³ History of SCD in a close relative, especially a sibling, often prompts more aggressive treatment, but this approach is not supported by clinical data¹⁴ and may simply reflect the clinician's (and family's) desire to prevent further tragedy at any cost.

It is possible that death of a sibling may be a marker of a more severe mutation, and, thus, a higher risk. However, LQTS patients demonstrate variable penetrance within families, with a wide range of QT intervals and symptoms.^{15,16} It is not known whether death of a sibling is an independent risk factor, or whether risk can be assessed adequately using an individual's own clinical characteristics. To test the hypothesis that the death of a sibling is a risk factor for death or aborted cardiac arrest (ACA) in patients with LQTS, we performed a multivariate analysis on subjects in the International Long QT Registry.

METHODS

All probands and first- and second-degree relatives of probands in the International Long QT Registry with QTc ≥ 0.45 s and with data available for relevant covariates were included. Enrollment of probands in the Long QT Registry was done through physician or self-referral, between 1979 and 2006. The first person in a family (living or deceased) identified to the Registry as having LQTS, with ECG documentation of QTc > 0.44 s, was enrolled as the proband. An enrollment packet was mailed, including enrollment questionnaire and study consent form. Personal medical history and family history were obtained by mailed questionnaire and/or telephone interview. Whenever possible, a family tree documenting all first and second degree relatives of the proband was constructed. Family members were contacted through the proband (or proband's parent, in the case of a minor) and, with informed consent, provided their own personal medical history and often provided further details for the family tree. All probands were coded at entry into the study regarding any family history of LQTS, syncope or cardiac arrest, sudden cardiac death, congenital deafness, and any known genetic disease. The current study involved an analysis of clinical and electrocardiographic data obtained historically at enrollment in the Registry and updated annually. Informed consent was obtained for enrollment in the Registry and participation in clinical studies. The Registry study was approved by the University of Rochester Medical Center Institutional Review Board. Because many of the subjects in the International Long QT Registry are family members who are unaffected by LQTS, and because genotype data are available for only a minority of the subjects, we elected to exclude subjects with QTc < 0.45 s. This would exclude some genetically affected LQTS subjects from the study population but would include relatively few unaffected

subjects, and would constitute a higher-risk group, which is the relevant population in which clinicians most often require data to assist in risk stratification.

Data were obtained from birth, with follow-up censored at 40 years of age for this analysis. Patients were born between 1898 and 2005, with 61% born in 1960 or later. The primary end point was a severe event--ACA or LQTS-related death. The secondary endpoint was any cardiac event (syncope, ACA or LQTS-related death). ACA was defined as a cardiac arrest requiring external defibrillation. LQTS related death was defined as sudden, abrupt unexpected death (without recovery) not due to other known causes. Additionally, in subjects who received an ICD, data were collected to determine the time of the first appropriate shock. If detailed records were not available, the first shock of uncertain cause was considered appropriate.

Statistical analysis

Cox proportional hazards regression models were used to assess the predictive power of multiple covariates. The assumption of proportional hazards was assessed using covariate interactions with age; the age-gender interaction was found to be significant and was included in the model. Covariates examined included sudden, unexplained death of a sibling (brother or sister) believed secondary to LQTS, modeled as a time-dependent variable, baseline QTc prospectively divided (0.45–0.48s, 0.49–0.52s, and ≥ 0.53 s), gender-age interaction, history of syncope within 2 years and beyond 2 years, treatment with beta-blockers, and ICD implantation. Although death events were used in two ways (as a predictor when occurring in a sibling, and as an endpoint), at each moment in time, risk was evaluated using past and current (up to the moment) information. As an example of how death of a sibling was modeled as an age-dependent variable, consider a child “A” whose sibling “B” died when A was 5 years old. For the first 5 years of A’s life, he did not carry the potentially risk-bearing characteristic of having had a sibling who died. At age 5, when B died, A was moved into the new risk category. Beta-blocker usage and ICD treatment were also modeled as time-dependent covariates. This means that at each point in time (age), those receiving (for example) beta-blockers were compared with those not receiving beta-blockers within each covariate pattern. All models were stratified by the decade in which study patients were born to account for changes in the baseline hazard function for different calendar time-periods. The four stratification periods used were dates of births before 1970, 1970–1979, 1980–1989 and 1990 and later. This approach was used to help account for changes over time in the treatment protocol for LQTS as well as potential clinical differences in the patients enrolled in the Long QT Registry later in life, compared to younger, more recent enrollees.

History of syncope was divided into recent (within 2 years) and remote (greater than 2 years) occurrence, based on previous studies that show that recent syncope (within the past 2 years) is a stronger predictor of risk of ACA/death than is a more remote history of syncope.¹⁷ The levels of statistical significance were set at a two-sided 0.05 level. QTc was calculated by Bazett’s formula. A Mantel-Byar graph¹⁸ was used for displaying cumulative risk for the time-varying covariate of sibling death. Standard Kaplan-Meier graphs were used to display the cumulative risk for QTc and gender. Age, rather than “time in the study”, was used as the time scale for the analyses: by following subjects from birth important data such as syncopal episodes could be captured even if these occurred prior to enrollment in the Registry.

RESULTS

There were 1915 subjects (including 640 probands, 862 first-degree relatives, and 413 second-degree relatives), of whom 270 had a sibling who died. The clinical characteristics of the subjects are shown in Table 1. Subjects with history of sudden death in a sibling were more likely to have a history of syncope ($p=0.017$) and they were more likely to be treated with a beta-blocker ($p=0.002$) or an ICD ($p=0.025$).

Among the 1915 study subjects, 829 had at least one cardiac event including 213 severe events (137 ACA and 76 LQTS-related deaths). Figure 1A is a Mantel-Byar graph showing the probability of a severe event in subjects with and without a history of death of a sibling, with sibling death modeled in a time-dependent manner. The figure is not adjusted for covariates. Although death in a sibling was associated with an increased risk of any cardiac event (predominantly syncope), as seen in Figure 1B, history of death in a sibling did not confer an increased risk of death or ACA.

In contrast, as shown previously in subset analyses involving children, adolescents, and adults, ^{17,19} QTc was highly predictive of severe events (ACA or death), as is shown in Figure 2A, of death alone (Figure 2B), and of all cardiac events (Figure 2C). The effect of gender was time-dependent. Whereas the risk of ACA/death and of any cardiac event was higher in boys than in girls, during late adolescence or early adulthood this relationship changed with a higher risk in women than in men (Figures 3A and 3B).

In the Cox proportional hazards multivariate analysis, history of death of a sibling was associated with increased risk of any cardiac event (hazard ratio 1.8, 95% CI 1.4–2.3, $p < 0.01$). However, death of a sibling was not associated with an increased risk of ACA or death (hazard ratio 1.1, 95% CI 0.7–1.8, $p = 0.58$) after adjustment for relevant covariates (Table 2). QTc ≥ 0.53 s was strongly associated with increased risk of any cardiac event (hazard ratio 2.4, 95% CI 2.0–2.8, $p < 0.01$) and with increased risk of ACA or death (hazard ratio 2.5, 95% CI 1.9–3.4, $p < 0.01$). A personal history of syncope was also strongly associated with risk of ACA or LQTS-related death (hazard ratio 6.1, 95% CI 4.4–8.4, $p < 0.01$). This risk was particularly high if syncope had occurred within 2 years (hazard ratio 11.3, 95% CI 8.0–15.8, $p < 0.01$), whereas a more remote history of syncope conferred a relatively modest risk (hazard ratio 3.3, CI 2.2–4.8, $p < 0.01$). Because genotype data were available in less than one third of the study population, we were unable to draw conclusions about the effect of genotype on ACA/death.

Overall, beta-blocker therapy was associated with a reduction in risk of ACA/LQTS-related death of about 50%. A more detailed analysis reveals that of the 350 subjects with QTc ≥ 0.53 s (of whom 228 or 65% were on beta-blocker therapy), 82 subjects (23%) had ACA/death (45 ACA and 37 deaths). Of the 37 subjects who died, 19 were on beta-blockers at the time of death; 16 of these patients had prior syncope. Of the 18 who died who were not on beta-blocker therapy, 10 had prior syncope.

DISCUSSION

In the current study, after adjusting for covariates, death of a sibling did not contribute to risk of ACA or LQTS-related death. Thus, it appears that severe symptoms in a close relative cannot be used as an indicator of personal risk for those family members affected by the same pathogenic substrate; rather, the incomplete penetrance and variable expressivity which are such consistent findings in LQTS^{15,16,20} preclude predicting severity of symptoms even in siblings. In contrast, an individual's own QTc, history of syncope and gender were strong predictors of risk.

The current study extends the findings of Kimbrough's study¹⁴ of 211 LQTS probands and 791 first degree relatives, in which severity of LQTS in the first-degree relatives was related to their own QTc, not to the severity of the probands' symptoms. The current study benefited from a larger number of events (829 cardiac events including 213 ACA/LQTS-related deaths vs. 67 cardiac events including 17 ACA/LQTS-related deaths in the earlier study). In addition, the current study took advantage of a newer, more sophisticated method of analysis, modeling death of a sibling as a time-dependent variable. Both study size and time-dependent modeling provided the potential for a more precise analysis.

The usefulness of QTc^{13,17,19,21,22} and personal history of syncope^{1,17,19} for predicting ACA/LQTS-related death is well-established (although evidence suggests that they may not predict well in LQT3).¹³ In the current large study of 1915 LQTS probands and first/second degree relatives (i.e. offspring, siblings, parents, aunts/uncles, and grandparents), QTc and personal history of syncope overwhelmed all other covariates as risk predictors of a severe event. Our finding of a time-dependent effect of gender is consistent with that reported previously.¹¹

It is not clear why subjects with a history of sibling death had a higher risk of all cardiac events (primarily syncope). It is possible that sibling death is a subtle marker of unmeasured risk. Alternatively, subjects with a history of sibling death may report syncope more vigilantly (whereas ACA/death is a more obvious endpoint). Reports of “syncope” in the Registry are characterized by abrupt onset and offset of loss of consciousness and probably represent arrhythmogenic syncope and not simply vasovagal and orthostatic events.

It may be argued that bereaved parents are not interested in relative risk but in the absolute risk of ACA/death in their remaining affected offspring. Assuming that all such offspring would be treated with beta-blockers, we analyzed the risk of ACA/death over a 5-year period that started at the time of their sibling’s death, for asymptomatic surviving affected siblings on beta-blocker therapy. There were 50 such subjects (40 with QTc 450–480 ms; 11 with QTc 490–520 ms; and 6 with QTc $\geq$ 530 ms). No ACA or LQT-related deaths occurred within this five-year period in the asymptomatic surviving siblings on beta-blocker therapy.

A potentially serious limitation of this study is that subjects with history of death in a sibling were more aggressively treated both with beta-blocker medication and with ICDs. This may have decreased the incidence of severe events in such subjects. So, even though history of sibling death did not contribute to risk of severe events in this study, it is possible that such an effect was masked by more aggressive therapy. We attempted to ascertain whether ICD implantation, more aggressively used in subjects with history of death in a sibling, influenced the outcome of this study. There were 189 subjects (out of 1915) who received an ICD, 140 of whom received an ICD before follow-up was censored due to ACA or age 41. Of these, follow-up ICD data were available in 137 (98%). When the primary endpoint of a severe event was redefined to include not only ACA and LQT-related death but also an appropriate shock or a shock of unknown appropriateness, the total number of endpoints increased from 213 to 229. Even so, sibling death was not predictive of the risk of reaching this endpoint.

Although we were able to incorporate beta-blocker use into the Cox model and although we verified that the disproportionate use of ICD implantation in the sibling-death group did not mask a higher risk of long QT-associated death, we were unable to exclude a protective effect of, for example, more consistent advice about avoiding QT-prolonging medications, competitive sports, and other triggers of torsades de pointes. While we acknowledge (and cannot correct for) the bias toward more aggressive treatment of the subjects with a history of death in a sibling, we recommend beta-blocker therapy and consistent advice for nearly all patients with long QT syndrome considered to be at some level of increased risk. In this study, subjects with a history of sibling death were more likely to be treated with (appropriate) beta-blocker therapy. The clinician must take care not to under-treat subjects without a history of sibling death.

The effects of beta-blockers in any registry-based study must be interpreted with caution. In 1985 Schwartz and Locati demonstrated that anti-adrenergic therapy was associated with a meaningful reduction in 15-year mortality of patients with LQTS presenting with syncope (from 53% to 9%).⁵ Since that time, beta-blockers have been the mainstay of treatment in LQTS, although several investigators^{7,8,23,24} have reported a substantial rate of beta-blocker

failure among high-risk patients with a history of ACA, syncope despite beta-blockers, or LQT3. In the current study, overall there was a 50% reduction in risk associated with the use of beta-blocker. Evaluation of beta-blocker efficacy in a registry-based analysis (rather than a randomized trial) is inherently limited because clinicians assign beta-blocker therapy to patients whom they believe to be at particularly high risk. Thus, beta-blocker use may become a surrogate marker of high risk. Despite this possible bias, we found a striking and significant benefit of beta-blocker therapy (see table 2).

CONCLUSIONS

In this study, a history of death of a sibling prompted more aggressive treatment (primarily beta-blocker therapy) but did not appear to add to risk of death or ACA (or appropriate ICD shock) among family members with LQTS. Subjects with and without history of sibling death should receive appropriate beta-blocker therapy and advice about avoiding triggers of torsades de pointes. Although the death of a sibling is tragic and understandably produces an emotionally charged setting when evaluating the rest of the family, the decision to implant an ICD should be based on an individual's own risk characteristics (QTc, gender, and history of syncope) and not solely on history of sibling death.

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REFERENCES

1. Moss AJ, Robinson J. Clinical features of the idiopathic long QT syndrome. *Circulation* 1992;85:1140–1144. [PubMed: 1345816]
2. Keating MT, Sanguinetti MC. Molecular genetic insights into cardiovascular disease. *Science* 1996;272:681–685. [PubMed: 8614827]
3. Chiang CE, Roden DM. The long QT syndromes: genetic basis and clinical implications. *J Am Coll Cardiol* 2000;36:1–12. [PubMed: 10898405]
4. Ackerman MJ. Cardiac channelopathies: it's in the genes. *Nat Med* 2004;10:463–464. [PubMed: 15122246]
5. Schwartz PJ, Locati E. The idiopathic long QT syndrome: pathogenetic mechanisms and therapy. *Eur Heart J* 1985;6:103–114. [PubMed: 2867907]
6. Schwartz PJ, Priori SG, Cerrone M, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. *Circulation* 2004;109:1826–1833. [PubMed: 15051644]
7. Dorostkar PC, Eldar M, Belhassen B, et al. Long-term follow-up of patients with long-QT syndrome treated with β -blockers and continuous pacing. *Circulation* 1999;100:2431–2436. [PubMed: 10595956]
8. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of β -blocker therapy in congenital long-QT syndrome. *Circulation* 2000;101:616–623. [PubMed: 10673253]
9. Zareba W, Moss AJ, Daubert JP, et al. Implantable cardioverter defibrillator in high-risk long QT Syndrome patients. *J Cardiovasc Electrophysiol* 2003;14:337–341. [PubMed: 12741701]
10. Moss AJ, Schwartz PJ, Crampton RS, et al. The long QT syndrome. Prospective longitudinal study of 328 families. *Circulation* 1991;84:1136–1144. [PubMed: 1884444]
11. Locati EH, Zareba W, Moss AJ, et al. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome - Findings from the international LQTS registry. *Circulation* 1998;97:2237–2244. [PubMed: 9631873]
12. Zareba W, Moss AJ, Locati EH, et al. Modulating effects of age and gender on the clinical course of long QT syndrome by genotype. *J Am Coll Cardiol* 2003;42:103–109. [PubMed: 12849668]

13. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003;348:1866–1874. [PubMed: 12736279]
14. Kimbrough J, Moss AJ, Zareba W, et al. Clinical implications for affected parents and siblings of probands with long-QT syndrome. *Circulation* 2001;104:557–562. [PubMed: 11479253]
15. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome - Clinical impact. *Circulation* 1999;99:529–533. [PubMed: 9927399]
16. Benhorin J, Moss AJ, Bak M, et al. Variable expression of long QT syndrome among gene carriers from families with five different HERG mutations. *Ann Noninvasive Electrocardiol* 2002;7:40–46. [PubMed: 11844290]
17. Hobbs JB, Peterson DR, Moss AJ, et al. Risk of aborted cardiac arrest or sudden cardiac death during adolescence in the long-QT syndrome. *JAMA* 2006;296:1249–1254. [PubMed: 16968849]
18. Mantel N, Byar D. Evaluation of response-time data involving transient states: an illustration using heart transplant data. *J Am Stat Assoc* 1974;69:81–86.
19. Sauer A, Moss A, McNitt S, et al. Long QT Syndrome in Adults. *J Am Coll Cardiol* 2007;49:329–337. [PubMed: 17239714]
20. Vincent GM, Timothy KW, Leppert M, et al. The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. *N Engl J Med* 1992;327:846–852. [PubMed: 1508244]
21. Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. *Am J Cardiol* 1993;72:23B–25B.
22. Zareba W, Moss AJ, Le Cessie S. Risk of cardiac events in family members of patients with long QT syndrome. *J Am Coll Cardiol* 1995;26:1685–1691. [PubMed: 7594104]
23. Priori SG, Napolitano C, Schwartz PJ, et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. *JAMA* 2004;292:1341–1344. [PubMed: 15367556]
24. Chatrath R, Bell CM, Ackerman MJ. Beta-blocker therapy failures in symptomatic probands with genotyped long-QT syndrome. *Pediatr Cardiol* 2004;25:459–465. [PubMed: 15534720]

Abbreviations

ACA, aborted cardiac arrest; CI, confidence interval; ICD, implantable cardioverter defibrillator; LQTS, long QT syndrome; SCD, sudden cardiac death.

A

B

Figure 1.

Mantel-Byar graphs showing time-dependent cumulative probability of ACA/LQT-Death (A) and of any cardiac event (B) in the absence of versus following the death of a sibling. This analysis accrues patients over time in the sibling death group, and thus the early events, when relatively few patients are at risk, impact the trajectory of the curve somewhat disproportionately. For this type of graph, only the total number of available subjects at birth is provided, since sibling death is a time-varying risk factor.

Figure 2.

A. Cumulative probability of ACA/LQT-death by QTc range. The numbers below the graph represent subjects at risk in each QTc range for each age. The numbers in parentheses show the rate of ACA/LQT-death at each age.

B. Cumulative probability of LQT-death by QTc range. The numbers below the graph represent subjects at risk in each QTc range for each age. The numbers in parentheses show the rate of LQT-death at each age.

C. Cumulative probability of any cardiac event by QTc range. The numbers below the graph represent subjects at risk in each QTc range for each age. The numbers in parentheses show the rate of any cardiac event at each age.

Figure 3.

Cumulative probability of ACA/LQT-death (A) and of any cardiac event (B) by gender. The numbers below the graph represent subjects at risk in each gender category at each age. The numbers in parentheses show the rate of ACA/LQT-death (A) and of any cardiac event (B) at each age.

Table 1**Clinical Characteristics**

Characteristics	Total	Sibling Death	No Sibling Death
# of Subjects	1915	270	1645
Female, %	61	65	61
Data at Enrollment			
Age, yrs	26±20	27±18	26±20
QTc, sec	0.493±0.047	0.492±0.046	0.493±0.048
PR, sec	0.148±0.027	0.150±0.026	0.148±0.027
QRS, sec	0.080±0.017	0.079±0.016	0.080±0.017
Heart Rate, BPM	78.2±22.3	74.5±18.2	78.8±22.8
Therapy, %			
Beta-blockers	50.34	58.89	48.94
Pacemaker	6.95	9.26	6.57
Sympathectomy	3.55	4.81	3.34
Defibrillator	9.92	13.70	9.30
Age at Last Contact, yrs	29.32±12.43	32.75±10.95	28.75±12.57
1st Cardiac Event, %	43.29	49.26	42.31
Syncope	39.58	47.04	38.36
ACA	2.66	1.48	2.86
LOTS-Related Death	1.10	0.74	1.16
Age at first event, yrs	14.2±9.4	15.8±9.2	13.9±9.4
Ever Cardiac Event, %			
Syncope	40.42	47.04	39.33
ACA	7.15	4.81	7.54
LOTS-Related Death	4.75	4.44	4.80

Table 2
Risk of Aborted Cardiac Arrest or LQT-Related Death

	Hazard Ratio	95% CI	P Value
QTc $\geq$ 0.53s : QTc $<$ 0.53s	2.54	1.91 – 3.37	<0.01
Syncope 0–2 years : No Syncope	11.26	8.00 – 15.84	<0.01
Syncope $>$2 years : No Syncope	3.26	2.21 – 4.81	<0.01
Beta Blocker	0.47	0.32 – 0.68	<0.01
ICD Implantation	0.13	0.02 – 0.96	0.045
Death of Sibling	1.14	0.72 – 1.79	0.58

Gender and gender X time covariates were also included in the models.