

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION



Congenital Long-QT Syndromes: Who's at Risk for Sudden Cardiac Death?

Charles I. Berul

Circulation 2008;117:2178-2180

DOI: 10.1161/CIRCULATIONAHA.108.772053

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

Copyright © 2008 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/cgi/content/full/117/17/2178>

Subscriptions: Information about subscribing to *Circulation* is online at
<http://circ.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Congenital Long-QT Syndromes Who's at Risk for Sudden Cardiac Death?

Charles I. Berul, MD

The congenital long-QT syndromes (LQTS) were initially described approximately 50 years ago.¹⁻³ The principal events are syncope, seizures, and ventricular tachycardia, characteristically torsade de pointes. Most often, this arrhythmia is self terminating, producing a syncopal episode; however, LQTS is responsible for a significant proportion of sudden cardiac deaths (SCDs) in young people without structural heart disease, estimated to have an incidence of approximately 1 in 2500 and causing thousands of deaths annually.⁴⁻⁶ Characteristic ECG signs of LQTS include QT-interval prolongation and T-wave abnormalities. The heart rate-corrected QT interval (QTc) can range from 370 to >700 ms, clearly overlapping that of normal individuals, and a single ECG may not manifest the stereotypical features.⁷⁻⁹ Some patients have a normal or borderline QTc at rest but prolongation with exertion or β -adrenergic stimulation. Provocative testing with exercise or catecholamine infusion may improve the sensitivity of LQTS clinical detection.⁹⁻¹¹ The inciting triggers are somewhat mutation-specific. Patients with potassium channel mutations typically have episodes during physical or emotional stress, whereas those with sodium channel defects have more events with bradycardia and during sleep.¹²⁻¹⁵ Symptoms, including syncope or SCD, can manifest anytime from the neonatal period to adulthood. Because risk stratification is still being refined, it is often recommended that most LQTS patients be treated with β -adrenergic blocking medications, but a diagnostic challenge is deciding who needs more specific or aggressive therapies. Interventions for LQTS include implantation of a permanent pacemaker or implantable cardioverter defibrillator (ICD), as well as consideration of left cardiac sympathetic denervation. If interventional therapy is warranted, what procedures are right for which patients, and when is the optimal time to intervene?¹⁶ The competing risks of the disease versus potential complications from the procedures or devices often increase the complexity of the clinical decision-making rationale.

Articles p 2184 and 2192

Over the past few decades, the International Long-QT Syndrome Registry has been enormously successful in pro-

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Department of Cardiology, Children's Hospital Boston, and Department of Pediatrics, Harvard Medical School, Boston, Mass.

Correspondence to Charles I. Berul, MD, Senior Associate in Cardiology, Children's Hospital Boston, 300 Longwood Ave, Boston, MA 02115. E-mail charles.berul@cardio.chboston.org (*Circulation*. 2008;117:2178-2180.)

© 2008 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>
DOI: 10.1161/CIRCULATIONAHA.108.772053

spectively enrolling many LQTS families from multiple countries. From this effort, several important findings have been reported, including the impact of age, gender, and genotype on outcomes in this large collection of LQTS patients.^{17,18} The International LQTS Registry has attempted to hone risk stratification by dividing its patient cohort into discrete age groups and has recently reported findings for adolescent and young adult patients.^{19,20} In the current issue of *Circulation*, Goldenberg and colleagues from the International LQTS Registry now separately report the findings from the youngest age cohort (children <13 years old)²¹ and the oldest age cohort (adults >40 years old).²²

LQTS Risk Stratification in Children

In the present report about LQTS in children,²¹ the authors have reviewed data submitted from contributing centers on >3000 children who were enrolled before their teenage years, focusing predominantly on fatal or near-fatal events. They identified clinical risk factors of marked QTc prolongation (>500 ms) in boys and syncope in both boys and girls to be significant predictors of aborted cardiac arrest or SCD during childhood. The syncope association with risk was time-dependent, because more recent syncope portended a higher hazard ratio than a remote history of syncope. Girls accounted for 63% of the children in the registry, and they had a slightly but statistically significant longer baseline QTc. Despite this, boys had a markedly higher rate of events (5% for boys, 1% for girls). These clinical risk factors persisted even when analyzed separately by genotype. Interestingly, a family history of SCD did not portend a higher likelihood of events during childhood, regardless of genotype.

Congenital deafness was also associated with serious adverse events, but segregated with syncope, and was therefore not found to be an independent risk factor. The total rate of serious events was quite low. Somewhat surprisingly, although the vast majority of the patients in the registry were already diagnosed with LQTS, and β -blockers have been shown to be safe and effective, only 21% of the children were being treated with a β -blocker, including some who had discontinued medication therapy. Treatment with a β -blocker reduced the risk of aborted cardiac arrest or SCD by approximately half in this pediatric cohort. A very small number of children received other antiarrhythmic medications, <2% received a pacemaker, 1% received an ICD, and 1% underwent left cardiac sympathetic denervation.

These findings are consistent with other series evaluating children with LQTS.²³⁻²⁵ Most studies of pediatric and young adult patients with LQTS show a higher risk of serious events, including SCD, with longer QTc values, history of syncope, or aborted SCD. The use of cardiac rhythm man-

agement devices, particularly ICDs, has grown substantially, even among younger and smaller patients with LQTS.^{26,27} Although it would seem logical that a positive family history of SCD is a surrogate for a malignant mutation, this has not been borne out as a higher independent risk factor for SCD in the present or in previous studies of children with LQTS.

The present report from Goldenberg and colleagues confirms a low mortality rate, with only 53 events (not all fatal) during nearly 12 years of follow-up in 3015 children with LQTS, which yields an annual serious event rate of 0.15%. One wonders whether this number could be reduced even further if more of the children in the registry were adequately treated with β -adrenergic blocking medications. When this event rate is countered against the potential complications related to ICD implantation and lead failure in children,^{26–29} the short- and long-term risks of interventional device therapy in low-risk LQTS children might outweigh the perceived benefits, which emphasizes the importance of the present report and highlights the continued need for improved risk stratification. Although the ICD clearly has life-saving value, it is not for everyone, and the majority of patients with LQTS can be treated effectively with β -blocker monotherapy.

LQTS in Adults After Age 40

In the companion report, Goldenberg and colleagues present their findings from the International LQTS Registry from adults >40 years of age.²² This likely completes the registry's series of age-related publications, along with the prior reports describing adolescents and young adults with LQTS. In the present report, the authors attempt to assess whether adults with LQTS who have lived to 40 years have a continued risk for serious cardiac events, including SCD. They assessed data from 2759 subjects 41 to 75 years old, stratified by QTc, gender, and age group (41 to 60 compared with 61 to 75 years). They defined patients with a QTc \geq 470 ms as "electrocardiographically affected," QTc of 440 to 469 ms as "borderline," and <440 ms as "electrocardiographically unaffected." Comorbidities were also examined to evaluate for competing risks of death. Because these patients have a higher risk of death due to any cause overall than the children and the younger LQTS populations studied, the authors used firm end points of either aborted cardiac arrest that required defibrillation or all-cause mortality. Even after age 40 years, patients with LQTS and a prolonged QTc continued to have a substantial risk of aborted cardiac arrest or SCD, particularly in the middle-age stratum (41 to 60 years old). Women with higher QTc intervals had more events than those without significant QTc prolongation, whereas the event rate was similar among men regardless of QTc range. Similar to the data in the children, recent syncope was a predictor of serious adverse events in affected patients, with a nearly 10-fold hazard ratio. β -Blockers were used in 25% of patients, more so in those with a longer QTc. A trend toward lower mortality was observed in the older patients treated with β -blockers, which could obviously be due to several different protective mechanisms. After age 60 years, the risk of death due to LQTS competes with other cardiovascular and noncardiac comorbidities that may lead to death. Among patients receiving ICD therapy, 15% experienced at least 1 appropriate

shock, and the authors concluded that ICD implantation in LQTS patients >40 years of age should be considered for primary prevention in high-risk individuals who remain symptomatic despite adequate β -blocker treatment and for secondary prevention after an aborted cardiac arrest. Data were limited on the utility of left cardiac sympathetic denervation, which was performed in only 9 patients in this adult LQTS population. Among the 871 genotyped patients, a mutation was identified in 62%. Those with a positive mutation had a significantly higher mortality rate, particularly those with an LQT3 mutation, although they comprised just 46 subjects. Taken together, these results in adults >40 years of age suggest a continuing risk for serious events, with some similarities in risk stratification to prior studies reported for younger adults, including QTc, gender, and genotype.^{12,30–33}

Summary

These 2 clinical series highlight the importance of long-term surveillance and data collection. The identification of risk factors to improve stratification of patients with more precision is crucial, because not all patients with LQTS will clearly benefit from invasive treatments. It is clear from the present series and others that the majority of patients can be managed safely and effectively with medical therapies and trigger avoidance. The selection of the high-risk patient who may benefit from interventional therapies such as left cardiac sympathetic denervation or cardiac rhythm management devices must be balanced carefully with the risk of arrhythmic sudden death. Congenital LQTS is clearly not 1 homogeneous syndrome but rather related syndromes with clinical, genetic, and phenotypic heterogeneity. The International LQTS Registry has proved invaluable for the rich data set that continues to provide interesting findings to help manage patients of all ages with LQTS.

Disclosures

Dr Berul has received research support from Medtronic and Boston Scientific. He is a consultant for Medtronic, Johnson & Johnson, and Novartis Pharmaceuticals.

References

1. Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the QT interval, and sudden death. *Am Heart J*. 1957;54:59–68.
2. Romano C, Genrme G, Pongiglione R. Aritmie cardiache rare dell'eta pediatrica. *Clin Pediatr*. 1963;45:656–683.
3. Ward OC. A new familial cardiac syndrome in children. *J Irish Med Assoc*. 1964;54:103–106.
4. Schwartz PJ. The long QT syndrome. *Curr Probl Cardiol*. 1997;22:297–351.
5. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, Hall WJ, Weitkamp L, Vincent GM, Garson A Jr. The long QT syndrome: prospective longitudinal study of 328 families. *Circulation*. 1991;84:1136–1144.
6. Roden DM. Long-QT syndrome. *N Eng J Med*. 2008;358:169–176.
7. Vaglio M, Couderc JP, McNitt S, Xia X, Moss AJ, Zareba W. A quantitative assessment of T-wave morphology in LQT1, LQT2, and healthy individuals based on Holter recording technology. *Heart Rhythm*. 2008; 5:11–18.
8. Vyas H, Hejlik J, Ackerman MJ. Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: diagnostic accuracy of the paradoxical QT response. *Circulation*. 2006;113:1385–1392.
9. Mönnig G, Eckardt L, Wedekind H, Haverkamp W, Gerss J, Milberg P, Wasmer K, Kirchhof P, Assmann G, Breithardt G, Schulze-Bahr E.

- Electrocardiographic risk stratification in families with congenital long QT syndrome. *Eur Heart J*. 2006;27:2074–2080.
10. Berul CI, Sweeten TL, Hill SL, Vetter VL. Provocative testing in children with suspect congenital long QT syndrome. *Ann Noninvasive Electrocardiol*. 1998;3:3–11.
 11. Vincent GM, Jaiswal D, Timothy KW. Effects of exercise on heart rate, QT, QTc and QT/QT2 in the Romano-Ward inherited long QT syndrome. *Am J Cardiol*. 1991;68:498–503.
 12. Moss AJ, Zareba W, Hall WJ, Schwartz PJ, Crampton RS, Benhorin J, Vincent GM, Locati EH, Priori SG, Napolitano C, Medina A, Zhang L, Robinson JL, Timothy K, Towbin JA, Andrews ML. Effectiveness and limitations of β -blocker therapy in congenital long-QT syndrome. *Circulation*. 2000;101:616–623.
 13. Hofman N, Wilde AA, Kääh S, van Langen IM, Tanck MW, Mannens MM, Hinterseer M, Beckmann BM, Tan HL. Diagnostic criteria for congenital long QT syndrome in the era of molecular genetics: do we need a scoring system? *Eur Heart J*. 2007;28:575–580.
 14. Tan HL, Bardai A, Shimizu W, Moss AJ, Schulze-Bahr E, Noda T, Wilde AA. Genotype-specific onset of arrhythmias in congenital long-QT syndrome: possible therapy implications. *Circulation*. 2006;114:2096–2103.
 15. Schwartz PJ. The congenital long QT syndromes from genotype to phenotype: clinical implications. *J Intern Med*. 2006;25:39–47.
 16. Stephenson EA, Berul CI. Electrophysiological interventions for inherited arrhythmia syndromes. *Circulation*. 2007;116:1062–1080.
 17. Zareba W, Moss AJ, Locati EH, Lehmann MH, Peterson DR, Hall WJ, Schwartz PJ, Vincent GM, Priori SG, Benhorin J, Towbin JA, Robinson JL, Andrews ML, Napolitano C, Timothy K, Zhang L, Medina A; International LQTS Registry. Modulating effects of age and gender on the clinical course of long QT syndrome by genotype. *J Am Coll Cardiol*. 2003;42:103–109.
 18. Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Robinson JL, Priori SG, Benhorin J, Locati EH, Towbin JA, Keating MT, Lehmann MH, Hall WJ. Influence of genotype on the clinical course of the long-QT syndrome. *N Engl J Med*. 1998;339:960–965.
 19. Sauer AJ, Moss AJ, McNitt S, Peterson DR, Zareba W, Robinson JL, Qi M, Goldenberg I, Hobbs JB, Ackerman MJ, Benhorin J, Hall WJ, Kaufman ES, Locati EH, Napolitano C, Priori SG, Schwartz PJ, Towbin JA, Vincent GM, Zhang L. Long QT syndrome in adults. *J Am Coll Cardiol*. 2007;49:329–337.
 20. Hobbs JB, Peterson DR, Moss AJ, McNitt S, Zareba W, Goldenberg I, Qi M, Robinson JL, Sauer AJ, Ackerman MJ, Benhorin J, Kaufman ES, Locati EH, Napolitano C, Priori SG, Towbin JA, Vincent GM, Zhang L. Risk of aborted cardiac arrest or sudden cardiac death during adolescence in the long-QT syndrome. *JAMA*. 2006;296:1249–1254.
 21. Goldenberg I, Moss AJ, Peterson DR, McNitt S, Zareba W, Andrews ML, Robinson JL, Locati EH, Ackerman MJ, Benhorin J, Kaufman ES, Napolitano C, Priori SG, Qi M, Schwartz PJ, Towbin JA, Vincent GM, Zhang L. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. *Circulation*. 2008;117:2184–2191.
 22. Goldenberg I, Moss AJ, Bradley J, Polonsky S, Peterson DR, McNitt S, Zareba W, Andrews ML, Robinson JL, Ackerman MJ, Benhorin J, Kaufman ES, Locati EH, Napolitano C, Priori SG, Qi M, Schwartz PJ, Towbin JA, Vincent GM, Zhang L. Long-QT syndrome after age 40. *Circulation*. 2008;117:2192–2201.
 23. Etheridge SP, Sanatani S, Cohen MI, Albaro CA, Saarel EV, Bradley DJ. Long QT syndrome in children in the era of implantable defibrillators. *J Am Coll Cardiol*. 2007;50:1335–1340.
 24. Schwartz PJ, Spazzolini C, Crotti L, Bathen J, Amlie JP, Timothy K, Shkolnikova M, Berul CI, Bitner-Glindzic M, Toivonen L, Horie M, Schulze-Bahr E, Denjoy I. The Jervell and Lange-Nielsen syndrome: natural history, molecular basis, and clinical outcome. *Circulation*. 2006;113:783–790.
 25. Taggart NW, Haglund CM, Tester DJ, Ackerman MJ. Diagnostic miscues in congenital long-QT syndrome. *Circulation*. 2007;115:2613–2620.
 26. Berul CI, Van Hare G, Kertesz NJ, Dubin AM, Cecchin F, Collins KK, Cannon BC, Alexander ME, Triedman JK, Walsh EP, Friedman RA. Results of a multicenter retrospective implantable cardioverter defibrillator registry of pediatric and congenital heart disease patients. *J Am Coll Cardiol*. 2008;51:1685–1691.
 27. Stephenson EA, Batra AS, Knilans TK, Gradaus R, Balagi S, Dubin AM, Rhee EK, Thøgersen AM, Walsh EP, Berul CI. A multicenter experience with novel implantable cardioverter defibrillator configurations in the pediatric and congenital heart disease population. *J Cardiovasc Electro-physiol*. 2006;17:41–46.
 28. Alexander MA, Cecchin F, Walsh EP, Triedman JT, Bevilacqua LM, Berul CI. Implications of implantable cardioverter defibrillator therapy in congenital heart disease and pediatrics. *J Cardiovasc Electro-physiol*. 2004;15:72–76.
 29. DeMaso DR, Lauretti A, Spieth L, Van der Feen JR, Jay KS, Gauvreau K, Walsh EP, Berul CI. Psychosocial factors and quality of life in children and adolescents with implantable cardioverter defibrillators. *Am J Cardiol*. 2004;93:582–587.
 30. Moss AJ, Zareba W, Hall WJ, Schwartz PJ, Crampton RS, Benhorin J, Vincent GM, Locati EH, Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. *N Engl J Med*. 2003;348:1866–1874.
 31. Topilski I, Rogowski O, Rosso R, Justo D, Copperman Y, Glikson M, Belhassen B, Hochenberg M, Viskin S. The morphology of the QT interval predicts torsade de pointes during acquired bradyarrhythmias. *J Am Coll Cardiol*. 2007;49:320–328.
 32. Brink PA, Crotti L, Corfield V, Goosen A, Durrheim G, Hedley P, Heradien M, Geldenhuys G, Vanoli E, Bacchini S, Spazzolini C, Lundquist AL, Roden DM, George AL Jr, Schwartz PJ. Phenotypic variability and unusual clinical severity of congenital long-QT syndrome in a founder population. *Circulation*. 2005;112:2602–2610.
 33. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. *N Eng J Med*. 2003;348:1866–1874.

KEY WORDS: Editorials ■ arrhythmia ■ genetics ■ pediatrics ■ risk factors ■ death, sudden ■ long-QT syndrome