JOURNAL OF INSURANCE MEDICINE

J Insur Med 2003;35:196–200

CASE STUDY

Assessment for Congenital Long QT Syndrome

Wayne F. Heidenreich, MD

A 29-year-old male presented for an evaluation of his risk for having congenital long QT syndrome. Despite being asymptomatic and having a normal QTc interval on the resting ECG, a suggestive family history was an indication for a thorough cardiac evaluation. A geneticist reviewed this workup and recommended against genetic testing. While up to 10% of affected carriers of a congenital long QT syndrome gene mutation can be asymptomatic with a normal QTc, consideration of all of the clinical factors allowed for further risk stratification. The evaluation of an ECG for the long QT syndrome includes calculating a corrected QT interval for the heart rate and assessing the T-waves for morphology associated with this syndrome.

Address: Northwestern Mutual, 720 E. Wisconsin Avenue, Milwaukee, WI 53202.

Correspondent: Wayne F. Heidenreich, MD.

Key words: Long QT syndrome, QT interval, electrocardiography, life insurance.

CASE PRESENTATION

A 29-year-old male applied for $1,000,000 of term insurance. In the application, he admitted to seasonal allergies, an office visit for lower back strain, and a normal ECG by his primary care physician. In the Family History section, he noted no medical problems in his 59-year-old father, 62-year-old mother, and a 28-year-old sister. Per the admitted application history, a younger brother died at age 18 of ''questionable heart disease.''

On physical exam, his height was 6'2'', weight 180 lbs, with a BMI of 23. His pulse was 72 and regular. The blood pressure averaged 107/78. The physical exam was normal with clear lungs and no murmur heard.

The insurance ECG was interpreted as normal with a sinus rhythm of 51 and no arrhythmia. The blood glucose, fructosamine, BUN/creatinine, liver enzymes, albumin/globulin, and urinalysis were all normal. The total cholesterol/HDL was 165/73 mg/dL with fasting triglycerides 70 mg/dL.

The attending physician's records revealed additional history. Medical care was obtained at a tertiary care referral center. Three years prior to application, at age 26, the insured applicant presented for a general medicine assessment of his risk of sudden death. His 18-year-old brother had sudden death while working at a summer music festival helping to park cars. He had become involved in a verbal altercation when he suddenly collapsed and never responded to immediate CPR and resuscitation efforts delivered by onlooking medical personnel. There was no known health problem and an autopsy showed no anatomic heart disorder. The family history obtained by the general medicine physician was also positive for a ''question of QT syndrome'' in a distant cousin.

An ECG and echocardiogram was ordered and a referral made to a cardiologist. The cardiology consultant further delineated a history of participation in soccer through the college years with no symptoms of palpita-

tions, presyncope, syncope, or unusual dyspnea. The resting ECG was normal, with a normal sinus rhythm of 58 bpm, normal ST- and T-wave morphology, and a QTc of 0.390 seconds. The echocardiogram was normal without evidence of asymmetric septal hypertrophy or right ventricular hypertrophy. The cardiologist confirmed a concern over the risk for long QT syndrome due to the family history with ''recent data showing carriers of the gene can present with normal ECGs.'' Further cardiology evaluation included a MRI of the heart, 24-hour Holter monitor, an exercise treadmill test, and a referral to a geneticist for consideration of genetic testing.

Follow-up cardiology notes document the MRI of the heart was normal without evidence by imaging of right ventricular dysplasia. The exercise treadmill showed a peak heart rate of 191 during Stage V of the Bruce protocol. The report notes no ectopy, arrhythmia, or ischemic changes. During exercise the QT interval shortened normally with increasing heart rate, and there were no changes in T-wave morphology. The 24-hour Holter monitor showed a sinus rhythm between 45 and 150 with an average rate of 68. There were rare PVCs and no supraventricular ectopic beats.

The geneticist was able to further develop a family history of 2 grandchildren of a paternal great uncle dying suddenly as teenagers in addition to a second cousin with the long QT syndrome. The geneticist concluded that the normal workup made it unlikely that the patient had long QT syndrome but did recommend that all family members have ECG screening. Genetic testing was not recommended for the patient as it ''would only be appropriate to begin with an affected family member.''

There was no other follow-up medical care for review.

The resting ECG obtained for insurance application was reviewed in light of this history. It showed a sinus rhythm of 50 bpm. The QT interval of 0.400 seconds when corrected for heart rate was 0.357 seconds (QTc). The T-wave morphology appeared normal.

CASE DISCUSSION

The congenital long QT syndrome was first described in 1957 in a family in which several children with congenital neural deafness had recurrent syncope and death. The ECG's QT interval was prolonged and the family pedigree was consistent with an autosomal recessive inheritance, the Jervell and Lange-Nielsen syndrome. A more common familial syndrome without deafness and with an autosomal dominant inheritance was described several years later, the Romano-Ward syndrome.[1]

Currently, the prevalence of gene carriers for this inherited disease is estimated to be 1 in 10,000 persons. This disease is estimated to cause 3000 to 4000 deaths a year in children and young adults.[2] In symptomatic disease, the mortality exceeds 20% in the first year after syncope without treatment and nearly 50% after 10 years. With treatment the mortality is 3% to 4% in the first 5 years.[3]

In the long QT syndrome, the prolonged QT interval is caused by mutations of transmembrane potassium and sodium ion channels of cardiac cells. This results in a prolonged ventricular repolarization phase and predisposes the individual to life-threatening ventricular arrhythmias like torsades de pointes, ventricular tachycardia, and ventricular fibrillation. A number of stimuli can bring on the arrhythmia, including exercise, emotional stress, sudden loud noise, and in some cases bradycardia in sleep. The ''acquired'' long QT syndrome may be caused by electrolyte abnormalities (hypokalemia, hypocalcemia and hypomagnesemia) or by medications that prolong ventricular repolarization.

With the extensive molecular genetic research now available, these ''congenital syndromes'' have become different diseases associated with mutations of 7 different genes located on 6 different chromosomes.[4] The gene mutations have been mapped to different sodium and potassium channels. In studies of families, these gene mutations have been correlated to different clinical character-

Table 1. Some Common Medications That Prolong the QT Interval

Antiarrhythmic drugs	Quinidine
	Procainamide
	Amiodarone
	Sotolol
Antimicrobial drugs	Erythromycin, azithromycin, clarithromycin
	Trimethoprim-sulfamethoxazole
	Ketoconazole, itraconazole
	Ciprofloxacin, levofloxacin, ofloxacin, moxifloxacin
	Chloroquine, mefloquine
Antihistamines	Terfenadine
	Astemizole
Psychotropic drugs	Thioridazine
	Tricyclic or tetracyclic antidepressants
	Haloperidol
	Risperidone
	Selective serotonin reuptake antidepressants
Miscellaneous	Very high dose methadone
	Cocaine

istics that include: incidence of first syncopal episode/cardiac arrest before age 10 and 40, types of triggers and mean corrected QT interval.[2,7] Given the complexity of the molecular structure of ion channels, mutations are now being described that only predispose to drug-induced prolongation of the QT interval.

This asymptomatic patient was considered for a possible inherited risk for long QT syndrome because of the sudden death of his 18-year-old brother who was exposed to a stressful emotional situation. As discovered by physicians over a period of months, several family members had sudden death at a young age. There was no ''definite'' diagnosis of long QT syndrome made in his brother, but the clinical history of sudden death together with the distant family history of long QT syndrome raised the concern of the proposed insured's physicians. Some forms of the congenital long QT syndrome have less than a 50% incidence of a first cardiac event before age 40.[2]

The normal MRI and echocardiogram were done to screen for right ventricular dysplasia and asymmetric septal hypertrophy. The 24-hour Holter showed some sinus bradycardia but insignificant ventricular ectopy. The history of being able to play demanding sports without symptoms was a good prognostic finding. This was clinically documented by a normal maximal exercise stress test with normal QT shortening with exercise and no arrhythmia.

The most reassuring finding was the normal corrected QT interval on the resting ECGs. The QT interval is prolonged at slower heart rates and there are several formulas proposed to adjust for this.[5] One common formula is the Bazett formula, in which the measured QT duration is divided by the square root of the R-R interval. This corrected QT (QTc) should be less than 0.440 seconds. QT intervals may be 10% longer in females. QTc intervals between 0.400 and 0.440 are borderline prolonged. Fortunately this proposed insured had a QTc $\leq$0.390 seconds. Most individuals with long QT syndrome have a QTc $\geq$0.450 seconds.

Provocative testing is sometimes used when the QTc is borderline prolonged. In exercise testing, the QT-interval should shorten appropriately with increasing heart rate. One gene mutation of the long QT syndrome is associated with abnormally long QT intervals with exercise, while another is associated with marked shortening. Electrophysiology

studies fail to induce arrhythmias with programmed stimulation. Adrenergic stimulation by epinephrine or isoproterenol infusion may produce U waves or arrhythmias.[3] These provocative tests are not definitive for making the diagnosis.

A scoring system of diagnostic criteria has been developed to assign points to clinical findings.[6] This system includes the ECG findings of a prolonged QTc, documented torsades de pointes, T-wave alternans (transient beat to beat changes in amplitude and shape), notched or bifid T-waves, and a low heart rate for age. Clinical history factors include a history of syncope with and without stress and congenital deafness. Family history risk is assessed for a family member with definite long QT syndrome and for an unexplained sudden cardiac death in an ''immediate'' family member under age 30. By this scoring system, this proposed insured was between low and intermediate probability with his family history.

Could this proposed insured still be an asymptomatic carrier of a mutation? Approximately 10% of carriers have QTc intervals less than 0.440 seconds. Only 2% of carriers with congenital long QT syndrome have *both* a normal QTc and normal morphology of the T-waves. In some families, penetrance of clinical disease for mutations may be as low as 25%.[2]

We can estimate a maximum mortality rate by estimating the insured is in a family with an autosomal dominant inheritance and variable penetrance at 50%. With the probability of carrying a mutation as an asymptomatic person with a negative ECG being 2%, the probability of this proposed insured having the carrier state is 1% or less.

The overall risk of sudden death in all heterozygotes for dominant long QT genes is approximately 0.5% per year (P1yr = 0.995 and P10yr = 0.951).[4] This yields a risk of less than 0.5–1.0 sudden deaths per 1000 lives over 10 years. This estimate gives an upper estimate of this man's risk given the many favorable features of his clinical history.

The clinical history and testing assured this proposed insured's physicians that further provocative testing, like epinephrine challenge testing, was not indicated. Genetic testing was not considered appropriate.

Beta adrenergic blockers, used to treat clinically diagnosed long QT syndrome, were not started. The patient was counseled to alert any treating physician regarding caution in using medications that prolong the QT like erythromycin and clarithromycin and antidepressants (also see Table 1).

SUMMARY

This 29-year-old male presented for evaluation for possible long QT syndrome because of suggestive family history. The congenital long QT syndrome is now being defined by 7 different gene mutations that affect different transmembrane ion channels and have different presentations and prognoses.[7,8,9] The risk for sudden death is significant. The asymptomatic presentation along with an ECG with normal QTc and T-wave morphology makes this patient a low probability for the long QT syndrome. Ten percent of affected patients are asymptomatic with a normal QTc interval, but only 2% of affected patients are asymptomatic with both normal QTc and normal T-wave morphology.[2] Penetrance has been estimated at 25%, and our case has a QTc well below even borderline prolongation of the QTc. This lowers the likelihood even further. This patient's risk can be safely assessed by his clinicians and by insurance medical directors using clinical criteria.

REFERENCES

1. Moss A. Long QT Syndrome. Contemporary Updates Linking Evidence and Experience. *JAMA.* 2003;289:2041–2044.
2. Wehrens X, Vos M, Doevendans P, et al. Novel Insights in the Congenital Long QT Syndrome. *Ann Intern Med.* 2002;137:981–992.
3. Roden D, Lazzara R, Rosen M, et al. Multiple Mechanisms in the Long QT Syndrome. *Circulation.* 1996; 94:1996–2012.
4. Keating M, Sanguinetti M. Familial Cardiac Arrhythmias. *The Metabolic & Molecular Bases of Inherited Disease.* Vol. III. 8th ed. McGraw-Hill Medical Publishing Division. 2001;203:5203–5222.

5. Al-Khatib S, Allen-LaPointe N, Kramer J, et al. What Clinicians Should Know About the QT Interval. *JAMA.* 2003;289:2120–2127.
6. Maron B, Moller J, Seidman C, et al. AHA Medical/Scientific Statement; Impact of Laboratory Molecular diagnosis on Contemporary Diagnostic Criteria for Genetically Transmitted Cardiovascular Diseases: Hypertrophic Cardiomyopathy, Long-QT Syndrome, and Marfan Syndrome. *Circulation.* 1998;98: 1460–1471.
7. Priori S, Schwartz P, Napolitano C, et al. Risk Stratification in the Long-QT Syndrome. *N Engl J Med.* 2003;348:1866–1874.
8. Daley S, Tranebjaerg L, Samson R, et al. Jervell and Lange-Nielsen Syndrome. *GeneReviews.* University of Washington, Seattle. 2003. Available at: www.genetests.org.
9. Vincent G. Romano-Ward Syndrome. *GeneReviews.* University of Washington, Seattle. 2003. Available at: www.genetests.org.