Consultation with the Specialist: The Long QT Syndrome

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Consultation with the Specialist

The Long QT Syndrome

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Case Studies

SK is a 12-year-old girl who was diagnosed 1 year ago with a generalized seizure disorder. Both her mother and maternal uncle had histories of seizures. She has been taking antiepileptic medication and has been seizure-free since the diagnosis. Six months after her seizure medication was discontinued, she died suddenly. Following her death, electrocardiograms (ECGs) revealed marked prolongation of the QT interval in the child's mother and maternal uncle.

JA, a 3-month-old boy, was diagnosed with gastroesophageal reflux disease and treated with ranitidine (a histamine-2-blocker) and cisapride (a promotility agent). He was brought to the emergency department after his mother found him cyanotic and unresponsive in his crib. Cardiac monitoring documented ventricular tachycardia. Cardioversion was successful, and follow-up ECG demonstrated a prolonged QT interval. Additionally, the serum level of cisapride was elevated.

JK is a previously healthy 10-year-old boy who was retrieved from the bottom of a public swimming pool and defibrillated at poolside from a torsade de pointes ventricular arrhythmia. He was racing his younger brother at the time of the near-drowning. ECGs obtained from the boy and available family members confirmed the diagnosis of congenital long QT syndrome in the boy and several others.

LA is a 15-year-old boy who has marked seasonal allergic rhinitis that has been well controlled for 3 years with astemizole (a nonsedating antihistamine). This fall he presented to his pediatrician after having multiple syncopal events over a 2-week period. After careful inquiry, the physician discovered that the boy had been taking ketoconazole for a short time for a presumed fungal infection. Suspecting acquired long QT syndrome, the pediatrician obtained an ECG, which demonstrated a prolonged corrected QT interval (QTc ~0.5 $sec^{1/2}$). The patient has remained free of syncope since discontinuing the ketoconazole. Further, management of his allergic rhinitis was changed to a "heart-friendly" antihistamine (eg, loratidine).

MK is a 2-year-old girl who is being evaluated for speech delay. She is the youngest of three living siblings. Another child died at 4 months of age from sudden infant death syndrome (SIDS). Hearing evaluation confirms the parent's suspicion that the child is deaf. ECGs identified the presence of Jervell and Lange-Nielsen syndrome. Both this child and her parents had prolonged QT intervals.

LD is a 6-week-old infant who was admitted to the hospital following paroxysmal coughing spells. Pertussis infection was established by nasopharyngeal culture, and the infant was started on a 14-day course of erythromycin. Ten days into the antibiotic therapy, a code 45 was called after her monitor indicated a ventricular arrhythmia and apnea. She was revived. A review of her medications showed that her reflux medication (cisapride) had not been discontinued when antibiotic therapy was initiated. An ECG confirmed the prolonged QT interval.

TA is a 17-year-old competitive athlete who collapsed suddenly during overtime of the state basketball championships. Hypertrophic cardiomyopathy was suspected, but an echocardiogram revealed no abnormalities. An ECG demonstrated a corrected QT interval of 0.44 $sec^{1/2}$ (borderline). However, closer inspection of the ECG revealed bizarre, notched T waves. The young man reported taking no medications, the drug screen was negative, and there were no electrolyte abnormalities. After the young man was stabilized, careful questioning revealed that this was not his first spell; he had had several previous syncopal episodes. He recalled passing out once when a teammate had "scared" him in the locker room. The initial negative family history was later amended to include a paternal uncle who had died at age 30 in an unexplained single-vehicle automobile accident. ECGs revealed clearly prolonged QT intervals in the patient's father and in one of the deceased uncle's children.

Introduction

These cases illustrate the myriad ways that the long QT syndrome (LQTS) conceals itself, lying in wait for the opportunity to transform the once peaceful, periodic lub-dub of the heart into a chaotic heap of asynchrony. Detective-like inquiry is required to unveil LQTS in individuals and families. LQTS crosses all pediatric disciplines, requiring the pediatrician to understand the syndrome, what triggers it, how and in whom this diagnosis should be sought and verified, and what can be done for those who harbor this ticking time bomb.

Definition

LQTS is so named because of its trademark feature on ECG (Fig. 1A) in which the QT interval measured from the start of the QRS complex to the end of the T wave is prolonged. In addition, the morphology of the T waves often is peculiar. With appropriate stimuli, the orderly periodicity of the heart degenerates into a polymorphic ventricular tachycardia known as torsade de pointes ("twisting of the points"), the hallmark arrhythmia heralded by LQTS. Individuals who have LQTS are susceptible to syncope, seizures, and sudden cardiac death.

Over the past 5 years, scientific breakthroughs have revealed the molecular basis for LQTS (Fig. 1B). Ion channels, fundamental membrane proteins that govern the electrical activity in the heart, are defec-

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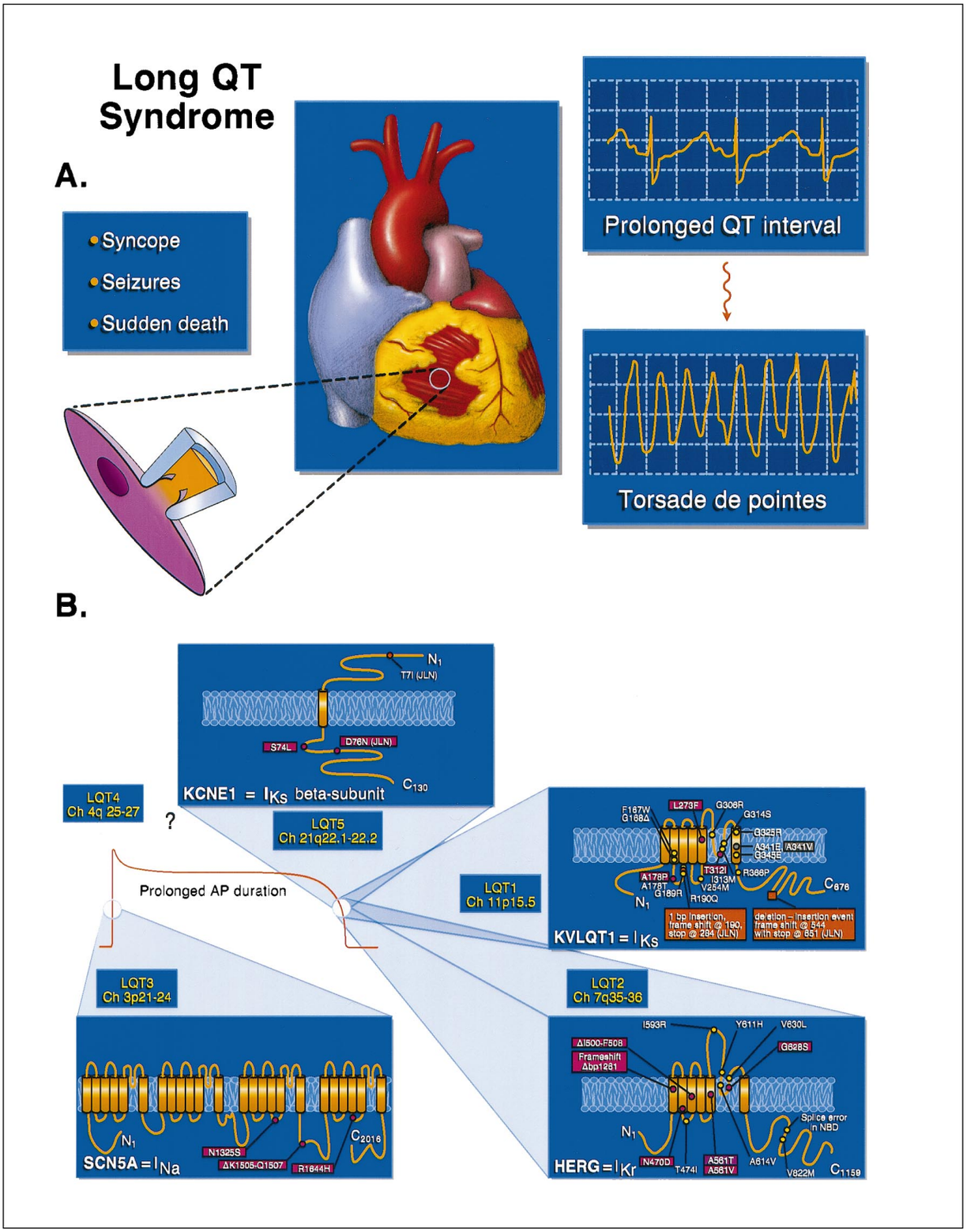

FIGURE 1. Molecular breakthroughs in LQTS. A. The hallmark clinical features of LQTS. Common presentations include syncope, seizures, and sudden death resulting from a ventricular arrhythmia, often of the torsade de pointes variety, stemming from an abnormally prolonged QT interval. B. The four ion channelopathies, including their linear topologies and identified mutations, that have been established as the molecular basis of LQTS. The designation of channel mutants is such that X###Y means that amino acid X has been replaced by amino acid Y at position ###. Mutations denoted in a red-violet rectangle represent ones that have been characterized functionally. Orange-highlighted mutations found in LQT1 and LQT5 represent the Jervell and Lange-Nielsen syndrome mutations.

tive. More than 50 genetic mutations in four critical cardiac ion channels have been demonstrated in inherited LQTS. Moreover, many drugs implicated in acquired LQTS alter the behavior of these same ion channels.

Etiology

Once considered an exceedingly rare condition, LQTS more correctly should be viewed as an unrecognized one. The diagnosis often remains concealed because the substantial variety of drugs, electrolyte abnormalities, and underlying medical conditions that can give rise to the acquired (iatrogenic) forms of LQTS are not disclosed (Table 1). Numerous drugs can cause QT interval prolongation and torsade de pointes. Antiarrhythmics, especially quinidine, are implicated most commonly in acquired LQTS, but other drugs have the potential to cause the syndrome, including certain antibiotics such as erythromycin, pentamidine, and trimethoprim-sulfamethoxazole; antifungal agents such as fluconazole, itraconazole, and ketoconazole; and promotility drugs such as cisapride. Concomitant use of the agents appears to carry particularly significant risk. Antidepressants such as amitriptyline can elicit cardiac arrhythmias. Patients who have eating disorders are at particular risk of LQTS and ventricular arrhythmias because of the combination of prolonged QT interval and severe bradycardia in many who suffer from anorexia nervosa.

Electrolyte derangements (low "lytes" cause long QT) also can yield the acquired LQTS. Syncope, seizures, or cardiac events that occur in the setting of brisk diuresis (acute hypokalemia); in head trauma that is associated with aggressive hyperventilation (acute hypokalemia); and in transplantation in which the immunosuppression regimen includes cyclosporin (chronic hypomagnesemia) should prompt the consideration of acquired LQTS and assessment of electrolyte status.

The congenital forms of LQTS often masquerade as epilepsy or vasovagal events or remain completely concealed. Key family facts, such as unexplained fatal accidents, SIDS, and familial epilepsy or familial fainting spells, either are not sought or, if elicited, are not considered pertinent in the evaluation of a child having syncope. The Jervell and Lange-Nielsen syndrome is very rare, occurring in 1 to 6 per 1 million individuals and inherited in an autosomal recessive manner. Four decades after the original clinical description of a Norwegian family in whom four of six children had prolonged QT interval, congenital sensorineural hearing loss, and recurrent syncope and three of the children died suddenly, the molecular basis (mutations in a cardiac potassium channel, KVLQT1, and its beta-subunit, minK) is now known (Fig. 1B, Table 2).

The other inherited form of LQTS, autosomal dominant in Romano-Ward syndrome, is not rare. Rather, it is vastly underdiagnosed. This syndrome initially was described in the early 1960s after noting families who exhibited QT prolongation, syncope, and sudden death. Today, Romano-Ward syndrome is viewed as a heterogeneous collection of at least six distinct molecular genotypes, with LQT1-3, 5 resulting from defective cardiac ion channels, LQT4 linked to chromosome 4q25-27 (no candidate gene has been identified), and LQT6 reserved for future assignments because several families remain unlinked.

Romano-Ward syndrome is estimated to occur in at least 1 in 10,000 individuals (up to 50,000 persons in the United States). There is no gender or ancestral preference. Furthermore, inherited LQTS is believed to account for 4,000 sudden deaths in children and young adults annually. To place this incidence in context, the Romano-Ward syndrome may occur three times as often as the most common childhood malignancy, acute lympho-

TABLE 1. Acquired Causes of Long QT Syndrome

Drugs
- Antianginals
- Antiarrhythmics
  - Class IA: disopyramide, procainamide, quinidine
  - Class III: amiodarone (rare), bretylium, dofetilide, N-acetylprocainamide, sotalol
- Antibiotics (erythromycin, pentamidine, trimethoprim-sulfamethoxazole)
- Antidepressants (tricyclics such as amitriptyline and desipramine)
- Antifungals (fluconazole, itraconazole, ketoconazole)
- Antihistamines (astemizole, terfenadine [removed from the market for this reason])
- Antipsychotics (haloperidol, respiridone, phenothiazines such as thioridazine)
- Lipid-lowering agents (probucol)
- Oral hypoglycemics (glibenclamide, glyburide)
- Organophosphate insecticides
- Promotility agents (cisapride)

Electrolyte Disturbances
- Acute hypokalemia (associated with diuretics and hyperventilation)
- Chronic hypocalcemia
- Chronic hypokalemia
- Chronic hypomagnesemia

Underlying Medical Conditions
- Arrhythmias (complete AV block, severe bradycardia, sick sinus syndrome)
- Cardiac (anthracycline cardiotoxicity, congestive heart failure, myocarditis, tumors)
- Endocrine (hyperparathyroidism, hypothyroidism, pheochromocytoma)
- Neurologic (encephalitis, head trauma, stroke, subarachnoid hemorrhage)
- Nutritional (alcoholism, anorexia nervosa, liquid protein diet, starvation)

blastic leukemia; one third as often as cystic fibrosis, the most common ultimately fatal genetic condition in Caucasians; and twice as often as phenylketonuria, a common disease revealed in routine newborn screening in Caucasians.

Presentation

The inherited LQTS can strike swiftly. One third of previously "healthy" children and young adults killed suddenly by LQTS may have sudden death as their first and last symptom. In general, approximately 60% of patients present with activity- or emotion-related symptoms—primarily syncope, seizures, and palpitations (Fig. 2). If these symptoms are related to the "fight, flight, or fright" response, LQTS should be considered strongly. Syncope, which accounts for one third of LQTS presentations, occurs in the setting of intense adrenergic arousal 60% of the time, with intense emotion and rigorous exercise implicated in more than 50% of cases. Interestingly, swimming appears to be a particular trigger (15%), as are abrupt auditory signals (8%), such as the doorbell, alarm clock, telephone, or smoke detector.

Inherited LQTS often is misdiagnosed as epilepsy because it presents with a generalized seizure in 10% of cases. It is not known how frequently a diagnosis of a primary generalized seizure disorder actually is LQTS (see the first case study). A careful history may reveal LQTS as the etiology of "epilepsy." In LQTS, the seizures are due to the cerebral ischemia that results from the ventricular arrhythmia. Therefore, LQTS should be considered strongly in an adolescent or young

TABLE 2. Congenital Causes of Long QT Syndrome

Autosomal Dominant (Romano-Ward Syndrome)
• Isolated susceptibility to ventricular arrhythmias, normal hearing
– LQT1 (30% to 50%)—chromosome 11p15.5—KVLQT1—potassium channel (I_{Ks})
– LQT2 (20% to 30%)—chromosome 7q35-36—HERG—potassium channel (I_{Kr})
– LQT3 (5% to 10%)—chromosome 3p21-24—SCN5A—sodium channel (I_{Na})
– LQT4 (?%)—chromosome 4q25-27—gene?
– LQT5 (?%)—chromosome 21q22.1-22.2—KCNE1—beta-subunit (minK) of potassium channel (I_{Kr} and I_{Ks})
– LQT6 (?%)—chromosome?
Autosomal Recessive (Jervell and Lange-Nielsen Syndrome)
• Associated with sensorineural hearing loss
– JLN1—chromosome 11p15.5—KVLQT1
– JLN2—chromosome 21q22.1-22.2—KCNE1 (minK)
LQTS With Syndactyly
• Inheritance?, gene?
Sporadic (?)

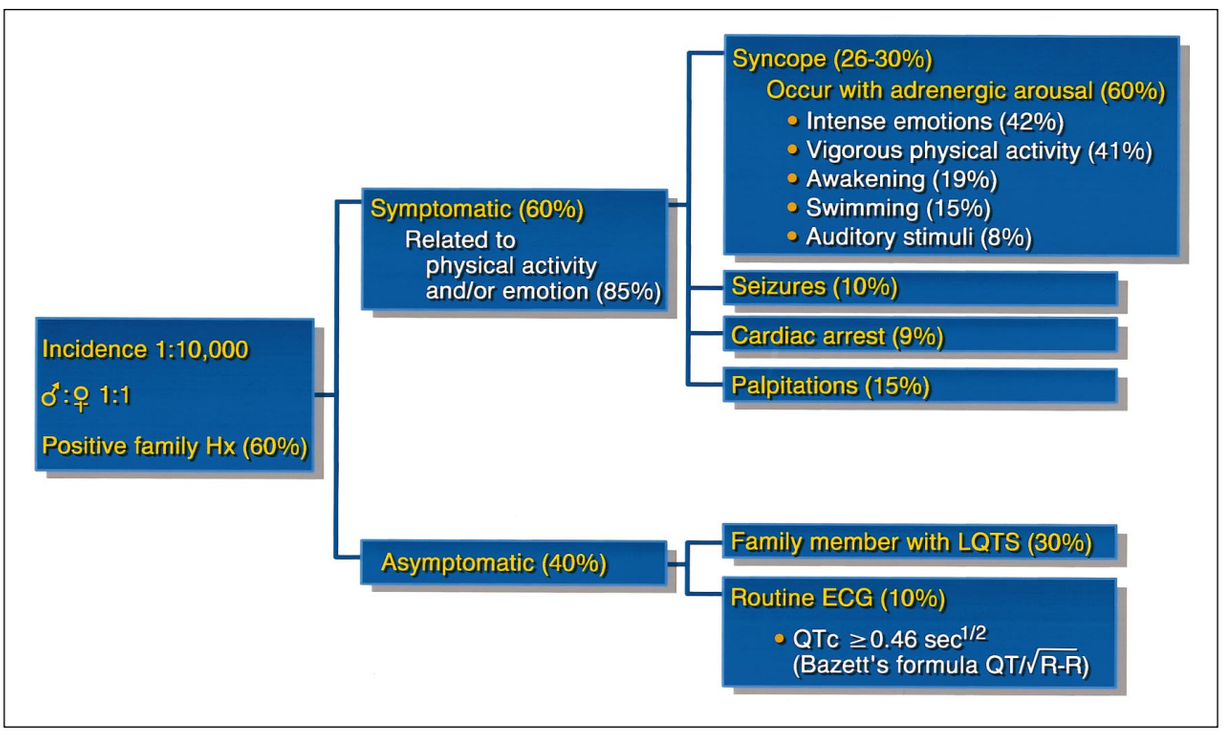

FIGURE 2. Clinical presentation of the LQTS. Family history is very common, as is the presence of symptoms, often adrenergic-precipitated episodes. Importantly, 40% of individuals who have LQTS are asymptomatic and are identified only after screening of family members of a symptomatic index case.

adult who describes the following sequence: dizziness, lightheadedness, blackouts, loss of consciousness, and then seizure. In young children who cannot provide such a chronology, a history of loss of consciousness preceding a seizure may suggest LQTS.

Importantly, more than one third of patients who have LQTS are asymptomatic. Most (75%) of these individuals are identified during routine screening of family members.

Evaluation

Figure 3 illustrates individuals in whom LQTS should be suspected and the evaluation they should receive. A 12-lead ECG is the current screening tool for identification of LQTS. If an ECG is obtained for this purpose, the physician must carefully inspect and determine the corrected QT interval (QTc), verifying the computer read-out. The QTc is derived by dividing the measured QT interval by the square root of the preceding R-R interval (Bazett's formula used to "correct" the QT interval for heart rate). However, it is impractical to recall this formula, and few readily know how to calculate the QTc based upon it.

Figure 3 provides a simple nomogram that enables the physician to measure the QT interval and preceding R-R interval in millimeters with a ruler/caliper and plot it on the chart. The QTc lines of 0.42 $sec^{1/2}$ and 0.46 $sec^{1/2}$ have been drawn. A plot falling on or above the top (solid, 0.46 $sec^{1/2}$) line is abnormal and represents LQTS with a positive and negative predictive value exceeding 90%. A plot landing in the borderline zone indicates a QTc between 0.42 $sec^{1/2}$ and 0.46 $sec^{1/2}$ and requires careful decision-making. At least 5% of known LQTS carriers (by genetic mutation) exhibit such a QTc. A borderline QTc in the setting of compatible symptoms or strong family history is consistent with LQTS. Figure 3 also highlights some of the peculiar T wave morphologies noted in LQTS. If such abnormalities are recognized on the ECG, the diagnosis of LQTS still is possible even with a borderline QTc. Finally, a plot falling below the bottom (dashed, 0.42 $sec^{1/2}$) line is not likely to be LQTS (~99% negative predictive value). Examining whether the measured QT interval is greater than 50% of the R-R interval has been suggested as a quick screen for LQTS, but this approach should be abandoned in preference to application of this QTc nomogram because it can result in a high rate of misclassification.

With this understanding of interpreting the ECG, determining the

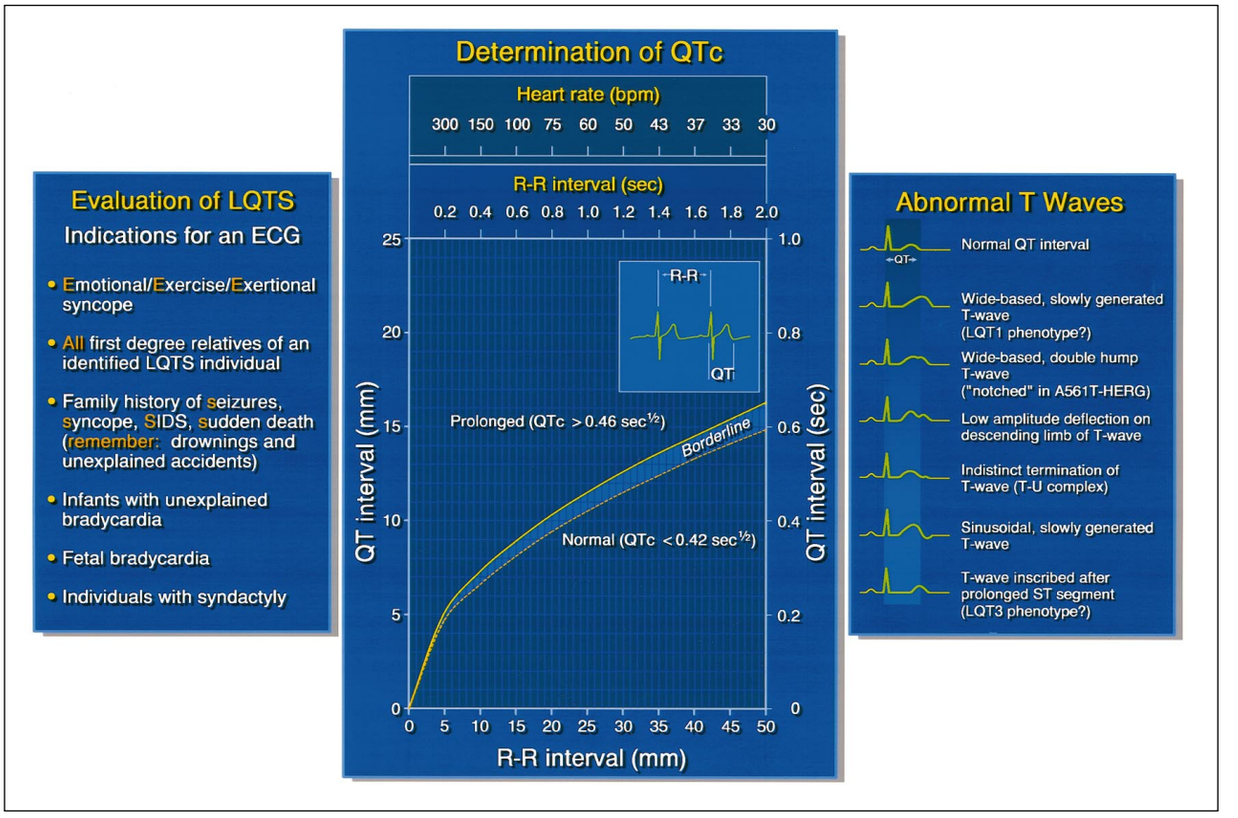

FIGURE 3. Evaluation of suspected long QT syndrome. The panel on the left lists scenarios in which a 12-lead ECG is indicated. The center panel provides an easily used QTc nomogram to confirm the accuracy of the computer-generated QTc and identify affected individuals. Using an ECG displayed at standard speed (25 mm/sec), the physician can plot the ruler intersection of the QT interval and RR interval measured in millimeters. Determinations falling on or above the QTc = 0.46 $sec^{1/2}$ line likely identify a patient who has LQTS and should be referred to a pediatric cardiologist. A patient who has compatible symptoms and a borderline ECG (plot falling between a QTc of 0.42 $sec^{1/2}$ and 0.46 $sec^{1/2}$) also should be referred. The panel on the right illustrates some T-wave abnormalities that can be seen in LQTS.

QTc, and inspecting the T waves, in whom should a physician suspect LQTS and thus obtain an ECG? Importantly, all patients who have syncope precipitated by emotions, exercise, or exertion and all first-degree relatives of a patient in whom LQTS is suspected must have an ECG. Any child who has a prolonged QTc ($\geq$0.46 $sec^{1/2}$) or a compelling borderline QTc (symptoms, family history, unusual T waves) should be referred to a pediatric cardiologist for further evaluation and treatment. Further evaluation may include a 24-hour ambulatory electrocardiographic monitor, a stress/exercise ECG, or repetition of the ECG in the sitting/standing position in an effort to bring out subtle abnormalities in ventricular repolarization. The cardiologist should coordinate screening of the identified patient's family, initiate appropriate therapy, and refer the family for genetic counseling.

Treatment

The 10-year mortality rate of untreated LQTS may exceed 50%; with therapy, this rate decreases to approximately 5%. Standard management options include beta-blocker therapy, implantation of a pacemaker and/or defibrillator, and a surgical procedure that involves a left cervicothoracic sympathetic ganglionectomy. All symptomatic patients should be treated with one or a combination of these therapies. The role of the primary physician is to monitor compliance, watch for troublesome side effects such as depression/mood changes and bronchospasm, and facilitate treatment adjustments in the face of breakthrough symptoms. In most cases, the presence of asthma has not precluded the successful use of beta-blocker therapy. It is vital to remind these patients to avoid medications known to trigger cardiac arrhythmias (Table 1). Finally, the physician often serves as the contact point when a previously asymptomatic but suspected LQTS family member becomes symptomatic. It is paramount to institute appropriate therapy promptly.

Unfortunately, the opportunity for such a lifesaving intervention is not always available, which has led some experts to suggest that every individual who has inherited LQTS, whether or not symptomatic, be treated. Proponents of this approach cite that nearly one third of individuals who die suddenly from LQTS have sudden death as their presenting symptom. In a large follow-up study of LQTS in children, two thirds of those experiencing sudden death were asymptomatic for more than 1 year prior to their death. Certainly, asymptomatic individuals whose presenting QTc exceeds 0.6 $sec^{1/2}$ should be treated because this degree of QT prolongation is a particularly poor prognostic factor. On the other hand, it may be difficult to justify treating the asymptomatic 50-year-old who just has been identified as part of a family screening. He or she already may have passed the test of time and is likely to have a "friendly" phenotype. Risks and benefits of treating asymptomatic family members must be weighed carefully by the primary physician, the cardiologist, and the family.

It also is important for the primary care provider to reinforce the no competitive sports policy because intense physical exertion can be deadly. Once properly treated, individuals who have LQTS can participate in recreational sports, but moderation and the presence of a "buddy" are key. Parents, teachers, and "buddies" must be made aware that a fainting episode or onset of seizure-like activity in a child who has LQTS requires immediate attention. If the episode persists for more than a few seconds, prompt activation of the 911 system is paramount because cardiopulmonary resuscitation and early defibrillation may be critical to saving the child's life. Because swimming is known as an arrhythmogenic trigger, affected individuals never should enter the water alone.

For acquired LQTS, intravenous magnesium is used to stabilize the heart's rhythm while offending drugs, electrolyte abnormalities, and underlying medical conditions known to precipitate torsade de pointes are sought and ameliorated.

Future Research

The decade of the 1990s has ushered in the molecular era for LQTS. Revelations that defects in fundamental cardiac ion channel proteins are responsible for this syndrome have created a molecular model of arrhythmogenesis. This model offers exciting prospects to address the menace of unexpected cardiac deaths due to ventricular arrhythmias, which account for some 300,000 deaths in the United States each year.

Hopefully, the next millennium will bring forth genotype-phenotype correlations as the natural clinical history of specific ion channel mutations is delineated. These discoveries will allow better patient counseling about particular risk factors for a sudden cardiac death and address the important question of which asymptomatic patients require treatment. For example, swimming may be found not to be a worrisome trigger in individuals who have mutation X.

In addition, LQTS will become a molecular diagnosis rather than a clinical, ECG-based diagnosis, which will permit presymptomatic diagnosis and early, appropriate intervention. Finally, the future holds great promise for genotype-targeted therapies. Individuals who have potassium channel mutants (LQT1, LQT2, and LQT5) may benefit from potassium channel openers; those who have defective cardiac sodium channels (LQT3) may do well with sodium channel blockers such as mexiletine.

Summary

The LQTS is no longer the rare "zebra" whose purpose is to ensure that trainees recall that deafness and sudden cardiac death may be related (Jervell and Lange-Nielsen syndrome). Over the past 10 to 20 years, the number of cases of inherited LQTS (Romano-Ward syndrome) has increased dramatically. It is doubtful that this reflects a true increase in incidence of disease due to a greater rate of sporadic gene mutations occurring in the heart or because of a rising incidence of consanguinity. Rather, the "incidence" of LQTS has risen

because of the emerging awareness of and respect for this electrical malady in the heart. Understanding the principal elements of the LQTS, knowing the types of presentations, and being able to identify its presence electrocardiographically will allow the astute physician to expose this silent killer.

SUGGESTED READING

Ackerman MJ. The long QT syndrome: ion channel diseases of the heart. *Mayo Clin Proc.* 1998;73:250–269

Ackerman MJ, Clapham DE. Ion channels: basic science and clinical disease. *N Engl J Med.* 1997;336:1575–1586

Ackerman MJ, Porter CJ. Identification of a family with inherited long QT syndrome following a pediatric near drowning. *Pediatrics.* 1998;101:306–308

Garson AJ, Dick M, Fournier A, et al. The long QT syndrome in children. An international study of 287 patients. *Circulation.* 1993;87:1866–1872

Keating MT. The long QT syndrome. A review of recent molecular genetic and physiologic discoveries. *Medicine.* 1996; 75:1–5

Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: an update. *Circulation.* 1993; 88:782–784

PIR QUIZ

7. In addition to a prolonged QT interval, an individual who has Jervell and Lange-Neilsen syndrome is *most* likely to have:
   A. Alopecia universalis.
   B. Cranial bruits.
   C. Hepatosplenomegaly.
   D. Rotary nystagmus.
   E. Sensorineural hearing loss.

8. The sport you are *most* likely to suggest that patients who have LQTS avoid is:
   A. Bicycling.
   B. Bowling.
   C. Ice skating.
   D. Swimming.
   E. Tennis.

9. The cut-off at which an individual has a 1% or less chance of having the LQTS is a corrected QT interval of *less* than:
   A. 0.42 $sec^{1/2}$.
   B. 0.43 $sec^{1/2}$.
   C. 0.44 $sec^{1/2}$.
   D. 0.45 $sec^{1/2}$.
   E. 0.46 $sec^{1/2}$.

10. A 16-year-old athlete has a syncopal episode immediately following a high school basketball game. Evaluation reveals a QTc of 0.52 $sec^{1/2}$. Which of the following family members would you recommend *must* have a screening electrocardiogram?
    A. All first-degree relatives.
    B. Brothers and male first cousins.
    C. Sisters and female cousins.
    D. Father and both grandfathers.
    E. Mother and both grandmothers.

IN BRIEF

Macrolides: Clarithromycin and Azithromycin

History of Macrolide Use in Pediatrics. Klein JO. *Pediatr Infect Dis J.* 1997;16: 427–431

Cost and Wastage of Antibiotic Suspensions: A Comparative Study for Various Weight Groups. Detar E, Mori G, Beaman D, Kumar A. *Pediatr Infect Dis J.* 1997; 16:619–622

A Prospective Study of the Impact of Community-based Azithromycin Treatment of Trachoma on Carriage and Resistance of *Streptococcus pneumoniae*. Leach AJ, Shelby-James TM, Mayo M, et al. *Clin Infect Dis.* 1997;24:356–362

The Effect of Changes in the Consumption of Macrolide Antibiotics on Erythromycin Resistance in Group A Streptococci in Finland. Seppälä H, Klaukka T, Vuopio-Varkila J, et al. *N Engl J Med.* 1997;337:441–446

Principles of Judicious Use of Antimicrobial Agents for Pediatric Upper Respiratory Tract Infections. Dowell SF, ed. *Pediatrics.* 1998;101(suppl):163–184

The newer macrolides clarithromycin and azithromycin have been used in pediatric patients for a few years, and it is appropriate to consider their roles in the antimicrobial armamentarium.

Erythromycin is the prototypic macrolide agent and still is the drug of choice for the treatment of *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila* disease. Clarithromycin has enhanced in vitro activity against group A streptococci and *Staphylococcus aureus* compared with erythromycin, and common pediatric pathogens such as pneumococcus, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* also are susceptible. It can be administered twice daily and does not require refrigeration. Clarithromycin is approved for use in pediatric patients who have sinusitis, acute otitis media, pneumonia, group A streptococcal pharyngitis and tonsillitis, and streptococcal or staphylococcal skin infections. Azithromycin is less active in vitro than erythromycin against staphylococci and streptococci, including pneumococcus. It has higher activity than either erythromycin or clarithromycin for *Haemophilus influenzae* and similar activity as clarithromycin for other common pediatric pathogens. However, azithromycin has unique pharmacokinetic properties, with a terminal phase half-life of approximately 68 hours. This half-life and the drug's ability to penetrate into phagocytic and other cells results in tissue levels persisting for 4 to 7 days after treatment is stopped. It is given once daily and also does not require refrigeration. Approved pediatric indications include pneumonia, acute otitis media, and pharyngitis/tonsillitis; the latter indication requires a higher dosing regimen.

In adults, both clarithromycin and azithromycin have many fewer gastrointestinal side effects than does erythromycin, but this difference is not as dramatic in children.

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