GENETICS IN YOUR PRACTICE

The Hereditary Long QT Syndrome

Long QT syndrome (LQTS) is an inherited channelopathy that affects the repolarizing potassium currents or causes prolonged depolarization via "leaky" sodium channels in the myocyte, resulting in a prolonged QT interval on an electrocardiogram. Hereditary LQTS classically affects family members in multiple generations, reflecting an autosomal dominant pattern of inheritance. Along with QT prolongation, these patients have symptoms of syncope and may develop polymorphous ventricular tachycardia (torsades de pointes) and sudden death.

BY PETER HULICK, M.D.

Diagnostic criteria, risk stratification, genotype-phenotype correlation, and clinical management recommendations have been guided by data from the International Long QT Syndrome Registry, which was established more than 25 years ago. The registry has more than 2,000 family members identified as having an LQTS-causing mutation.

Diagnosis

The prevalence of LQTS is estimated to be 1 in 2,000-5,000; however, the expressivity, or penetrance, of the syndrome is highly variable even within the same family. Diagnosis often hinges on documentation of a prolonged corrected QT interval (QTc) using Bazett's formula, which adjusts for heart rate.

ECG evaluation of first-degree relatives should be performed when an unexplained sudden cardiac death has occurred, particularly in a young adult. QTc values over 450 msec in adult men and over 470 msec in adult women are considered prolonged and should be investigated further. It is important to consider other potential causes of prolongation, such as certain medications.

Often the diagnosis of LQTS is not clear on initial evaluation, and a scoring system (Circulation 1993;88:782-4) is utilized to ascertain the probability of LQTS. The criteria incorporate ECG data, clinical history, and family history in determining a low, intermediate, or high probability of LQTS. The current criteria do not include the results of genetic testing, but such testing can be helpful in evaluating borderline cases.

Genetics

Currently 12 genes have been identified as causing LQTS and are designated LQT1-12. Most of the genes encode proteins that are subunits of the cardiac ion channels. Clinical testing is available for LQT1-12, and a causative mutation can be detected in approximately 70% of high-probability patients. Thus, negative results on genetic testing does not "rule out" LQTS, which is important to point out when counseling patients and their family members.

The majority of mutations have been identified in LQT1 (40%-55%), LQT2 (35%-45%), and LQT3 (2%-8%), which represent the genes KCNQ1, KCNH2, and SCN5A, respectively. Significant clinical and mutational data have been collected with respect to LQT1-3 to allow clinicians to begin incorporating this information into risk stratification and treatment plans, in addition to identifying asymptomatic family members as "at risk" individuals.

In patients with LQT1 mutations, cardiac events tend to occur during states of increased physical or emotional stress; arrhythmia is classically triggered by exercise, swimming, or sudden emotion. Those with LQT1 mutations are at highest risk during sympathetic activation, which probably explains why beta-blockers are most effective at preventing cardiac events in these patients. Similarly, LQT2 mutations confer a risk that emotional distress or a sudden loud noise (such as an alarm clock ringing) may trigger a cardiac event; patients with LQT2 mutations also tend to respond to beta-blocker therapy. Patients with LQT3 mutations are at risk of having cardiac events during nonemotional states such as sleep or rest. Relying on beta-blocker therapy for LQT3 is more controversial, especially as the lethality of the events may be higher for carriers of LQT3 mutations.

The type and location of the mutation contribute to differing risk levels and can explain some of the interfamilial variation. For example, in LQT1, a dominant-negative mutation (in which an abnormal gene product interferes with normal gene product's ability to function) conferred a twofold risk of cardiac events, compared with mutations causing haploinsufficiency of the protein (not enough protein produced for normal function). Mutations involving the transmembrane domain of the protein were associated with a higher risk of cardiac events in LQT1 patients.

Risk Assessment

Although clinical parameters remain the cornerstone of risk stratification, advances in genotype-phenotype correlation in LQTS are improving personalized risk assessment. Broadly, patients are categorized as low (QTc of 500 msec or less and no prior syncope), intermediate (QTc over 500 msec or prior syncope), or high risk (post–cardiopulmonary resuscitation or spontaneous torsades de pointes).

The categories represent the 5-year risk of cardiac events (aborted or sudden death) of 0.5% for low-risk, 3% for intermediate-risk, and 14% for high-risk patients. Data are emerging on adjustment of risk category based on LQT subtype. For example, a male with a QTc under 500 msec would be classified as low risk, but if he carried an LQT3 mutation, his risk would be adjusted upward to the intermediate category.

The risk of a life-threatening cardiac event changes with age and with the number and timing of syncopal events, and is influenced by gender and length of the longest QTc recorded (not necessarily initial QTc). These factors should be incorporated into an individual's risk assessment. Finally, family history of a premature sudden cardiac death is not an independent risk factor for a subsequent lethal event in another family member.

Management

The mainstay of therapy in patients with LQTS remains beta-blockers, particularly in LQT1 patients. It is important to ensure adequate dosage and compliance with beta-blocker therapy, and to avoid QT-prolonging drugs (www.qtdrugs.org).

The threshold to proceed to an implantable cardioverter defibrillator (ICD) varies from center to center, but ICDs are generally reserved for secondary prevention after a previous cardiac event, for primary prevention in high-risk individuals, and for patients who continue to have symptoms despite adequate beta-blocker therapy.

Minimally invasive, video-assisted, thoracic left cardiac sympathetic denervation procedures are being studied as potential treatment options. This type of procedure may benefit patients who have a history of appropriate ICD shocks or who have a prohibitive risk of morbidity with ICD placement. The procedure also may serve as a "bridge" to ICD implantation. ■

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Gene Variants Linked to Lipoprotein and Heart Disease

BY MARY ANN MOON

Two common variants in the lipoprotein(a) gene have been found to correlate with both plasma lipoprotein levels and the risk of coronary disease, according to Dr. Robert Clarke of the University of Oxford (England) and his associates.

The finding supports the hypothesis that lipoprotein plays a causal role in coronary disease.

The investigators examined genetic associations in coronary artery disease using data from the Precocious Coronary Artery Disease (PROCARDIS) Consortium multicenter case-control study. The study cohort included 3,145 patients from the United Kingdom, Italy, Sweden, and Germany who developed coronary artery disease before age 66 years and also had a similarly affected sibling, and 3,352 control subjects.

Genotyping was performed on participants' blood samples using a novel gene chip that was specifically designed to screen more than 48,000 single-nucleotide polymorphisms (SNPs) for 2,100 candidate genes thought to be potentially relevant to heart disease. "With this gene chip, we confirmed the previous identification of three chromosomal regions that were correlated with the risk of coronary disease: 6q26-27, 9p21, and 1p13," Dr. Clarke and his colleagues noted.

The 6q26-27 region showed the strongest association with coronary disease, and that region is known to include the gene for lipoprotein(a) (LPA).

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"We then used comprehensive SNP typing to characterize the spectrum of variation at the LPA locus and showed the independent relevance of several variants ... for both the Lp(a) lipoprotein level and the risk of coronary disease," the investigators wrote (N. Engl. J. Med. 2009;361:2518-28).

Two variants in particular (rs3798220 and rs10455872) together accounted for 36% of the variation in plasma lipoprotein levels among study subjects.

The investigators replicated these findings in separate cohorts from three other clinical trials of coronary disease, which included 4,846 cases and 4,594 control subjects.

"The linear dose-response relationship of the LPA variants with both the Lp(a) lipoprotein level and the risk of coronary disease provided compelling support for a causal role of an elevated plasma level of Lp(a) lipoprotein and the risk of coronary disease," the researchers said.

"One in six persons carries a variant LPA allele and thus has a risk of coronary disease that is increased by a factor of 1.5," they added. ■

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