Congenital Long QT Syndrome

Congenital LQTS is a genetic disorder characterized by abnormal cardiac repolarization producing QT prolongation on the ECG (corrected QT [QTc] >440 milliseconds in men and >460 milliseconds in women). It is a leading cause of SCD in the young.

Mutations in 16 genes that participate in cardiac repolarization have been identified in patients with LQTS. Mutations of *KCNQ1* (encodes the α-subunit of the I_{Ks} potassium channel) produce LQT1; mutations of *KCNH2* (encodes the α-subunit of the I_{Kr} potassium channel) produce LQT2; and mutations of *SCN5A* (encodes the α-subunit of the cardiac sodium channel) cause LQT3. Together, they account for 75% of cases of congenital LQTS.

Decreased outward potassium currents or increased inward sodium currents prolong action potential duration, predisposing to early afterdepolarizations and TdP, a specific type of polymorphic VT. Symptoms typically begin during adolescence and include syncope, seizures, and SCD. The arrhythmia triggers in LQTS are gene specific. Patients with LQT1 are at risk during high adrenergic states, such as exercise; arrhythmias in LQT2 are triggered by sudden noises such as alarms; and LQT3 patients are more likely to experience arrhythmias during sleep. The autosomal dominant Romano-Ward variant has a prevalence of 1 case in 2000 live births.

Chronic treatment is directed at prevention of SCD. Initial therapy includes avoidance of QT-prolonging agents and initiation of β-blockers in symptomatic patients and asymptomatic patients with significant QT prolongation. ICDs are recommended after resuscitation from a cardiac arrest and for recurrent syncope despite β-blockade. The acute treatment of TdP is different from that of other forms of VT because many antiarrhythmic agents prolong the QT interval and should therefore be avoided.

Brugada Syndrome

The Brugada syndrome is a genetic disorder predisposing to polymorphic VT and SCD. The ECG characteristically displays coving ST elevation in the right precordial leads, V_1 to V_3, and a right bundle branch block pattern. These electrocardiographic abnormalities may be dynamic, and they are characteristically exacerbated by fever and therapy that blocks sodium channels.

In most cases, the syndrome is linked to mutations in *SCN5A*, which encodes the cardiac sodium channel. Mutations result in a reduction in the sodium current. The mode of transmission is autosomal dominant. Patients typically have syncope or cardiac arrest, often occurring during sleep.

Although quinidine, by virtue of its ability to block transient outward potassium current (I_{to}), may have a therapeutic role, there are no established medical therapies to prevent VT in Brugada syndrome. Intravenous β-adrenergic stimulation with isoproterenol or a similar agent, by virtue of its ability to augment the sodium current, is potentially useful in the acute management of recurrent VT or VF in Brugada syndrome. Paradoxically, because of a protective effect of catecholamine stimulation, β-blockers are potentially harmful in patients with Brugada syndrome and should be avoided.

ICDs represent the only proven therapy for prevention of cardiac arrest. ICD therapy is recommended for secondary prevention of SCD. For high-risk patients with a spontaneous Brugada electrocardiographic pattern and syncope, primary prevention with an ICD is indicated.

Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT is a genetic disorder that alters myocardial calcium handling, resulting in exercise-induced polymorphic or bidirectional VT. Exercise-triggered syncope or SCD during childhood is the common presenting symptom. About 50% to 60% of patients have an inherited or sporadic autosomal dominant mutation affecting the cardiac ryanodine receptor gene *(RYR2)*, producing abnormal calcium-induced calcium release from the sarcoplasmic reticulum and intracellular calcium overload.

β-Blockers along with exercise restriction represent the primary therapy, although arrhythmia breakthrough is common. ICD therapy may be used for secondary prevention, although ICD shocks can produce catecholamine surges that may exacerbate the underlying arrhythmia. Left cardiac sympathetic denervation is useful in selected cases.

Acquired Long QT Syndrome

Environmental factors may prolong cardiac repolarization and produce QTc prolongation, leading to the development of early afterdepolarizations and TdP. Patients with acquired LQTS may have background genetics predisposing them to develop excessive QTc prolongation and polymorphic VT in response to electrolyte abnormalities (i.e., hypokalemia, hypomagnesemia, and hypocalcemia), bradycardia, and the use of QT-prolonging medications. Most QTc-prolonging drugs block the rapid component of the delayed rectifier potassium channel (I_{Kr}) encoded by the *KCNE2* gene. Drugs known to prolong the QTc interval are updated on an Internet registry. Therapy for acquired LQTS requires reversal of inciting physiologic factors and discontinuation of offending medications.

Genetic Testing for Channelopathies

Commercial laboratories offer genetic testing for congenital LQTS, Brugada syndrome, and CPVT. The yields of genetic testing vary from 25% for Brugada syndrome up to 80% for congenital LQTS. The limited sensitivity of current assays and the common finding of genetic variants of unknown significance represent ongoing challenges. Despite these considerations, cascade screening or screening of family members for a disease-causing mutation once characterized in a proband has been effectively used to identify mutation carriers.

Mutation-positive family members may benefit from prophylactic therapy. Reassurance for mutation-negative individuals is also valuable. Before ordering genetic testing, patients should be thoroughly informed of the risks, benefits, and limitations of testing. Genetic counselors ideally play an important advisory role.

For a deeper discussion on this topic, please see Chapter 65, "Ventricular Arrhythmias," in Goldman-Cecil Medicine*, 25th Edition.*