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Long qt syndrome: Genetic counseling and gene based therapy

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The long QT syndrome (LQTS) is a genetic disorder affecting ion channels of membranes of excitable cells, typically cardiac myocytes and occasionally the cells of inner ear which cover endolymphatic space. It is important to recognize the syndrome even though it contributes very less to the overall burden of sudden cardiac death (SCD). Unlike the common causes of SCD, LQTS is effectively treatable and preventable disorder. The affected patients are usually children and young adults with normal hearts and otherwise healthy. They have prolongation of QT interval on the ECG and are at risk for syncope, seizures and sudden cardiac death due to a malignant ventricular tachyarrhythmia called torsades-de-pointes (TdP).The events are usually triggered by exertion, swimming, emotion or auditory stimuli. Some of the patients in addition suffer sensorineural deafness. Comprehensive management of this inherited syndrome includes diagnosing and treating the proband and identifying and protecting affected family members by genetic counseling. The gratifying results of therapy based on type of genetic defect have been seen more consistently in the management of LQTS proband and asymptomatic relatives than any of the other genetic disorders of the heart and rhythm. Despite the plethora of advanced imaging, diagnostic, and genetic tests available today, the most important factor needed to establish a diagnosis of LQTS remains still the patient's overall clinical picture. As a rule, any individual with a personal or family history suspicious for LQTS should undergo a thorough cardiac evaluation including but not limited to a 12-lead ECG. The primary diagnostic characteristic of LQTS is a prolonged QT interval corrected for heart rate (QTc) on 12-lead ECG: QTc>450 ms in men and >460 ms in women.

Over the past 2 decades, 15 distinct LQTS-susceptibility genes (and hundreds of mutations), each encoding a critical component of cardiac ion channels have been identified. Mutations in KCNQ1 (LQT1), KCNH2 (LQT2), and SCN5A (LQT3) represent the most common causes of LQTS and collectively account for an estimated 60%-75% of genotype-positive LQTS cases. β-blockers and or left cardiac sympathetic denervation (LCSD) has proven extremely effective in LQT1. Although β-blockers remain first-line therapy for the treatment of LQT2, given the higher rate of life-threatening breakthrough cardiac events specifically resuscitated SCAs, ultimately, many high-risk patients with LQT2 require LCSD or, if clinically indicated, an ICD. As in LQT2, given the higher rate of breakthrough cardiac events while on β-blocker therapy, ultimately more patients with LQT3 may require LCSD or ICD implantation or both. β-blocker therapy alone is often insufficient for the LQTS subtypes such as JLNS, Ankyrin-B, Anderson-Tawil, Timothy, and Recurrent Infantile Cardiac Arrest Syndromes. Early initiation of combination therapy consisting of β-blockers, adjunct antiarrhythmic agents, LCSD, and ICD therapy should be strongly considered.