Long QT syndrome

Genetics

-15 genes; most common: KCNH2 (LQT2), KCNQ1 (LQT1), SCN5A (LQT3)

-AD; mostly inherited; de novo is rare; exception: Jervell and Lange-Nielsen syndrome (AR)

-20% with LQTS without variant in known genes

Clinical findings/Dysmorphic features

-Cardiac electrophysiologic disorder; QT prolongation and T-wave abnormalities on ECG

-Associated with tachyarrhythmias (ventricular tachycardia torsade de pointes [TdP])

-TdP is usually self-terminating --> syncopal event (fainting, most common symptom in LQTS)

-Events during exercise/emotional stress, less common during sleep, usually without warning

-In some instances, TdP degenerates to ventricular fibrillation and causes aborted cardiac arrest (if the individual is defibrillated) or sudden death

-50% of untreated individuals with a pathogenic variant in one of the genes have symptoms (one to a few syncopal events); most common from preteen years through the 20s

Etiology

-Prevalence of LQTS has been estimated at 1:2,500

Pathogenesis

-LQTS genes encode for potassium or sodium cardiac ion channels or interacting proteins

-LOF variants in potassium channels (K+) and gain of function in sodium channel (Na+)

-Abnormal ion function --> prolongation of cardiac AP and susceptibility of cardiac myocytes to early afterdepolarizations (EADs) --> ventricular arrhythmia, TdP

Genetic testing/diagnosis

-Multigene panel: KCNQ1 (30-35% of cases; Seq 98%, In/Del 2-3%); KCNH2 (25-30% of cases; Seq 98%, In/Del 2-3%); SCN5A (5-10% of cases; Seq 100%)