**EDITORIAL COMMENT**

The Congenital Long QT Syndrome

A Mask for Many Faces*

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For most of the latter half of the 20th century, after its discovery in 1957 (1), the congenital long QT syndrome (LQTS) was divided simply into 2 forms, the Jervell and Lange-Nielsen syndrome associated with deaf mutism and the Romano-Ward syndrome with normal hearing. On the basis of the early reports, both variants were considered adrenergic-sensitive for arrhythmogenesis. This perception provided the rationale for the effective therapies of that period—beta adrenergic receptor blockers (2) and left cardiac sympathectomy (3).

In the mid-to-late 1990s, a series of reports in rapid succession established that the basic clinical phenotype of prolonged QT interval and ventricular tachyarrhythmias with distinctive morphology (torsades de pointes) could result from mutations in 5 different genes encoding subunits of ion channels that conduct currents critically involved in repolarization (4–8). Four of the channel subunits form 2 ion channels that conduct outward repolarizing lysine potassium currents, $I_{Kr}$ (KCNQ1 and KCNE1) and $I_{Kr}$ (KCNH2 and KCNE2). The other subunit (SCN5A) transmits intense inward excitatory current and a low amplitude depolarizing inward norepinephrine sodium current that prolongs the plateau and delays repolarization. The numerous mutations since described in these genes have in common a prolongation of repolarization by a loss of function and reduction of current of the K channels or a gain of function of the Na channel causing enhanced late Na current. The simple 2-part classification has given way to a more complex gene-based classification that includes LQT1-6; JLN 1 and 2; LQT7, the Andersen syndrome (9); and LQT8, the Timothy syndrome (10). The LQT4 (Ankyrin B), LQT7 (KCNJ2), and LQT8 (CACNA1C) are more recently discovered genetic variants.

Scientists investigating the links between abnormal function of the mutant gene products and the clinical manifestations are advantaged by high-precision measurement of the functions (i.e., the ionic currents) of the normal and mutant ion channels and their components. In addition, the electrocardiogram has served as an accessible monitor of the global phenotypic expression of disturbed ventricular repolarization. The International LQTS Registry has been an invaluable resource of genotyped patients and families comprehensively studied and followed (11). Information about gene defects and their functional and clinical consequences has amplified exponentially.

Amid this abundance of information, a vexatious problem for the clinician has emerged: the wide variation among carriers of gene defects in the severity of the prolongation of repolarization, the response to provocative conditions (triggers), and the arrhythmia risk. The expanded knowledge of the functional consequences of mutations in the different genes and the variations in responses of these mutant gene products to pharmacological agents, internal conditions, and external triggers has provided a wider range of gene-specific therapeutic approaches involving pharmacotherapy and adjustments of lifestyle (12). However, because none of these approaches including the standard beta blockade has offered absolute protection, implantable cardioverter-defibrillator implantation is preferred for those who have failed other therapeutic measures or are judged to be at high risk (13). Consequently, risk assessment is a critical component of the clinician’s evaluation of family members or known mutation carriers.

Variable risk within the whole population of patients with the congenital long QT syndrome is inevitable. Repolarization is a complex process governed by the operation of multiple ion channels as well as other transport mechanisms. Each of the ion channels involved has distinctive properties and responses to various conditions. Mutations on different genes affect repolarization differently depending on the effect of the defective subunit on the function of the ion channel and the varying conductance of the channel throughout repolarization. The nature and severity of the abnormality of the specific involved current also depends on the site of the mutation on the gene (14) and, in some cases, coexistence of certain otherwise clinically insignificant alleles (15). The impact on repolarization of a specific genetic defect and its mutant ion channel is determined not only by the severity of impairment of the function of the channel but by the aggregate of the other processes controlling repolarization. Repolarization reserve denotes the capacity of other repolarizing currents to override the negative contribution of the mutant channel to repolarization (16).

Tachyarrhythmias associated with prolonged repolarization depend on triggering by early afterdepolarizations (EAD) that in turn depend on disorders of calcium (Ca)
transport induced by prolonged repolarization (17). Adrenergic stimulation enhances by multiple mechanisms Ca\textsuperscript{2+} loading of the myocyte, which promotes EAD formation (17). If \( I_{Ks} \) is intact, Ca\textsuperscript{2+} loading by adrenergic stimulation is mitigated by the abbreviation of the action potential duration by adrenergic \( I_{Ks} \) enhancement. In the genetic variants involving \( I_{Ks} \) deficiency, provocation of arrhythmias by adrenergic stimulation is more severe and beta adrenergic receptor blockers are more effective. In other variants, the role of adrenergic stimulation is not as prominent because \( I_{Ks} \) enhancement occurs.

The sustenance of torsades de pointes is likely the result of macroreentry in a milieu of dispersion of refractoriness due to heterogeneity of the distribution of ion channels and currents within the ventricular myocardium (18). Variation among individuals in the numerous factors involved in these tachyarrhythmia mechanisms adds to the complexity, by determining differing susceptibilities to lethal arrhythmias among affected individuals.

Against this background of complexity, the identification of useful risk predictors has been extraordinarily difficult (19). The degree of prolongation of the QTc interval has emerged as the most reliable single predictor of risk for LQT1 and LQT2, but its value in LQT3 is questionable, and it is undefined for other more rare forms. Gender predicts risk variably, depending on the genotype. Risk varies according to the specific gene involved and the site of the mutation on the gene. Even a single site mutation produces a highly variable phenotype of clinical severity among carriers, the phenomenon known as variable penetrance (20).

In this issue of the Journal, Schwartz et al. (21) address variable penetrance in a large set of South African families carrying a single mutation on KCNQ1. A previous study by this group reported that this mutation, KCNQ1-A341V, is a dominant negative mutation that produces a relatively severe clinical phenotype (22). The KCNQ1 mutations are the most sensitive to adrenergic triggers (23), because \( I_{Ks} \) is modulated by adrenergic stimulation.

Cognizant of adrenergic sensitivity of arrhythmogenesis in LQT1, Schwartz et al. (21) investigated sympathetic/autonomic activity as reflected in heart rate, heart rate variability, and baroreceptor sensitivity, and they screened for adrenergic receptor polymorphisms, attentive to those that might affect function. Comparing symptomatic and asymptomatic groups, they found that resting heart rates were higher in the symptomatic group, confirming a prior study. Heart rate variability was not significantly different in the 2 groups. Baroreceptor sensitivity was increased in the symptomatic group, a finding ostensibly at variance with prior studies demonstrating that increased baroreceptor sensitivity was associated with reduced arrhythmia risk after myocardial infarction.

The investigators postulate that mutation carriers with increased baroreceptor sensitivity are at greater risk, because they are more likely to experience more intense heart rate decelerations and longer diastolic intervals, which are known to predispose to EAD triggering. However, baroreceptor activation produces sympathetic withdrawal, which could mitigate the mechanisms for arrhythmogenesis. The authors suggest an alternative explanation. Higher baroreceptor sensitivity might indicate higher sympathetic tone, the withdrawal of which would cause greater slowing during baroreceptor activation. Higher heart rates and increased baroreceptor sensitivity would be linked as indicators of higher resting sympathetic activity, which plausibly could be associated with greater active sympathetic responses and greater arrhythmia risk.

They found a relationship between increased baroreceptor sensitivity and the expression of 2 polymorphisms that have been shown to enhance adrenergic activity. The ADRA2C-Del322-325 polymorphism causes reduced function of an alpha\textsubscript{2} adrenergic receptor, which would enhance norepinephrine release by reducing inhibitory feedback (24). The ADRB1-G389R polymorphism enhances coupling of the beta\textsubscript{1} adrenergic receptor to adenylyl cyclase and augments adrenergic stimulation (25). The finding of a correlation between these polymorphisms and baroreceptor sensitivity is intriguing and supportive of the inference that the higher baroreceptor sensitivity reflects higher sympathetic tone. However, the relationship of these polymorphisms to resting heart rates or to symptoms has not been determined.

Adrenergic stimulation was the first recognized risk factor in the congenital long QT syndromes. It is now recognized that its role in arrhythmogenesis is most prominent in LQT1, the most common form of the congenital long QT syndrome. However, it likely plays a variable role in other congenital long QT syndromes by affecting Ca transport and arrhythmogenesis. Additional studies of the activity of the adrenergic system and its genetic modifiers in the congenital long QT syndrome, especially LQT1, are warranted.

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