Prevention of Ventricular Arrhythmias in the Congenital Long QT Syndrome

Sami Viskin, M D, and Roman Fish, M D

Address
Department of Cardiology, Sourasky-Tel Aviv Medical Center, Sackler School of Medicine, Tel Aviv University, Weizman 6, Tel Aviv 64239, Israel. E-mail: viskin_s@netvision.net.il

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Introduction
The congenital long QT syndrome (LQTS) results from mutations in genes encoding for specific ion channels (located in the myocardial cell membrane) that are involved in the process of myocardial repolarization [1,2••,3,4]. Six different genotypes (including four genotypes involving distinct components of two potassium channels and one responsible for sodium channel malfunction) have been identified (Table 1), but additional mutations remain to be identified, because up to 50% of the families with clinically apparent congenital long QT syndrome do not link to any of the recognized genotypes [3].

The ensuing intracellular surplus of positive ions delays the ventricular repolarization, prolonging the QT interval. Furthermore, because other ion channels are voltage-dependent, any delay in repolarization prompts additional inward currents (most likely calcium currents). Consequently, the action potential not only fails to repolarize but also depolarizes again, creating characteristics “humps” in the action potential that are termed early afterdepolarizations (EADs). These EADs may reach threshold amplitude and trigger ventricular extrasystoles [4]. Complicating matters further, the myocardial cells in the deep or “mid” myocardium (thus termed M cells) are particularly sensitive to ion channel malfunction. The M cells display more repolarization delay and EADs than epicardial or endocardial cells [5] and the resulting heterogeneity of repolarization facilitates the propagation of multiple waves of reentry responsible for the distinctive arrhythmia of this disease: torsade-de-pointes [5,6].

Based on the mode of onset of the spontaneous arrhythmias, episodes of torsade de pointes can be classified as adrenergic-dependent or pause-dependent (Fig. 1) [4,7]. In pause-dependent torsade, a relatively long cycle, ie, a pause, invariably precedes the ventricular arrhythmias. In contrast, in adrenergic-dependent (tachycardia-dependent) torsade de pointes, the ventricular arrhythmias follow sinus tachycardia. For years, adrenergic-dependent torsade was equated with the congenital LQTS, whereas pause-dependent torsade de pointes was believed to occur primarily in the acquired LQTS [8–10]. More recent data, however, suggest that the majority of arrhythmias in the congenital LQTS (at least in adults) are actually pause-dependent [11,12••] and that adrenergic-dependent torsade de pointes predominates in more severe forms of the disease (including infants with arrhythmic storms and patients with deafness) [13].

Therapy of the Long QT Syndrome
Symptoms in the LQTS are caused by torsade de pointes, ranging from syncope (when the arrhythmia terminates spontaneously) to cardiac arrest (when torsade de pointes deteriorates to ventricular fibrillation). Life-long preventive therapy of these potentially lethal arrhythmias is therefore necessary. Merits and limitations of the different modes of therapy are shown in Table 2. It should be emphasized, however, that due to the rarity and high mortality of this disease, long-term controlled studies are not available for any of the therapeutic modalities proposed for the LQTS.
Drug Therapy

**β-blockers**

The association between arrhythmias and stress prompted the empiric use of β-blockers shortly after the first descriptions of the LQTS [14–16]. By 1975, Schwartz et al. [17] collected data on the effects of drug therapy in 203 patients reported by different authors. The apparent effect of β-blockers on survival was compelling: 41 (73%) of 68 patients left untreated and seven (64%) of 18 patients treated with miscellaneous drugs, but only five (6%) of 79 patients treated with β-blockers died [17]. This literature analysis had obvious limitations: the patients included in the different reports varied in regard to the severity of their disease and the duration of follow-up. Nevertheless, the difference in mortality observed among patients treated with and without β-blockers was of such magnitude (6% vs 56%) that β-blockers became the first-line of treatment for the congenital LQTS [17]. When the International LQTS Registry (formed by Schwartz, Moss, and Crampton in 1979) reported its first data, 96% of patients with symptomatic LQTS were getting β-blockers [18]. Subsequent reports from this registry consistently showed that β-blocker therapy is associated with a 0.41 relative risk for syncope or cardiac arrest (95% confidence interval, 0.21–