Indian Pacing and Electrophysiology Journal xxx (2017) 1–11

Contents lists available at ScienceDirect

Indian Pacing and Electrophysiology Journal

journal homepage: www.elsevier.com/locate/IPEJ

The congenital long QT syndrome Type 3: An update

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ARTICLE INFO

Article history:
Received 14 August 2017
Received in revised form
27 October 2017
Accepted 30 October 2017
Available online xxx

Keywords:
Long QT syndrome
Long QT syndrome-type-3
Torsade de Pointes
Electrocardiogram

ABSTRACT

Congenital long QT syndrome type 3 (LQT3) is the third in frequency compared to the 15 forms known currently of congenital long QT syndrome (LQTS). Cardiac events are less frequent in LQT3 when compared with LQT1 and LQT2, but more likely to be lethal; the likelihood of dying during a cardiac event is 20% in families with an LQT3 mutation and 4% with either an LQT1 or an LQT2 mutation. LQT3 is consequence of mutation of gene SCN5A which codes for the Nav1.5 Na^+ channel α-subunit and electrocardiographically characterized by a tendency to bradycardia related to age, prolonged QT/QTc interval (mean QTc value 478 ± 52 ms), accentuated QT dispersion consequence of prolonged ST segment, late onset of T wave and frequent prominent U wave because of longer repolarization of the M cell across left ventricular wall.

1. Introduction

LQT3 Romano-Ward (OMIM number #600163) is an autosomal dominant channelopathy (exceptionally can be with autosomal recessive inheritance) responsible for 7–10% of total LQTS that affect the chromosome 3(3 (3p21-24)) consequence of mutation of gene SCN5A which codes for the Nav1.5 Na^+ channel α-subunit, and electrocardiographically characterized by a tendency to bradycardia related to age, prolonged QT/QTc interval (mean QTc value 478 ± 52 ms), accentuated QT dispersion consequence of prolonged ST segment, late onset of T wave and frequent prominent U wave because of longer repolarization of the M cell across left ventricular wall. The late Na^+current (INa+) is due to the failure of the channel to remain inactivated. Therefore, it can enter a bursting mode, during which significant current enters abruptly when it should not. Transmural dispersion of repolarization is greatly amplified in LQTS. Disproportionate prolongation of the M-cell action potential (AP) contributes to the development of long QT intervals, wide-based or notched T waves, and a large transmural dispersion of repolarization, which provides the substrate for the development of a polymorphic ventricular tachycardia (PVT) closely resembling Torsade de Pointes (TdP). An early afterdepolarization (EAD)-induced triggered beat is thought to provide the premature ventricular contraction (PVC) that precipitates TdP. The T waves increases in bradycardias and in pauses and it may present alternating polarity with augmented risk of cardiac events (CEs) (mean 46%) of a bradycardia-triggered PVT called TdP by the French researcher François Dessertenne as well as for atrial fibrillation (AF). These CEs may result in recurrent, palpitation, syncope, seizure, sudden cardiac arrest (SCA) or sudden cardiac death (SCD), which occur predominantly at rest or during sleep without emotional arousal (≈65% of cases). These events can be treated gene-specific therapy for LQT3 with Na^+ channel blocking agents of Class IB (mexiletine, lidocaine); Class IC (flecainide) and the piperazine derivate ranolazine **(Ranexa®)** that may provide protection from the induction of TdP by inhibition persistent or late inward Na^+ current (I_{Na}) of a gain of function in the cardiac voltage-gated Na^+. In symptomatic patients receiving therapy, even after excluding patients who had a SCA before therapy, presence of macro-wave T alternans especially when present despite proper β-blocker therapy, and biallelic pathogenic variants or heterozygosity variants have indication for ICD implantation.

LQTS prevalence: The estimated prevalence of LQTS is

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Peer review under responsibility of Indian Heart Rhythm Society.

https://doi.org/10.1016/j.ipej.2017.10.011

Please cite this article in press as: Pérez-Riera AR, et al., The congenital long QT syndrome Type 3: An update, Indian Pacing and Electrophysiology Journal (2017), https://doi.org/10.1016/j.ipej.2017.10.011

approximately 1:2000 (0.05%) to 1:5000 in the general population [1]. This prevalence may be higher because 37% of genotype-confirmed LQTS patients may have concealed form (a normal-range QTc). LQT3, which is the third most common LQTS (7–10% of all cases of LQTS) represents ≈100 to 200 in general population.

LQTS incidence: In the United States, the incidence of congenital LQTS is estimated to be one in 7000–10,000 [2]. Consequently; if LQT3 represents 7–10% of all LQTS cases, this variant has an incidence of ≈720.

Sex: risk is higher among male LQT3 patients with a mutation than among female. Among LQTS patients, the risk of CEs is higher in males until puberty and higher in females during adulthood. The annual incidence of a first SCAUDDEN or SCD is highest among male patients with a mutation at the LQT3 locus (0.96 per year). Prolonged QTc and syncope predispose patients with LQT3 to life-threatening CEs. β-blocker therapy reduces the risk in females. Efficacy in males could not be determined conclusively yet [3]. This pattern is observed in both boy and girl. Wilde et al. described that there is not much difference and actually the number of lethal events is very small. According to the authors, that is the reason that the efficacy of beta blockers could not be found. Therefore, there is not a consensus about it yet.

Age: For patients older than 40 years, LQT3 patients have significantly more cumulative lethal arrhythmic events (35%) than LQT1 (14%), LQT2 (24%) and genotype-negative patients (10%) [4]. LQT3 carriers have infrequent CEs below age of 10 years. Murphy et al. [5] presented a SCN5A splice variant potentiates dysfunction of a novel mutation associated with severe fetal arrhythmia. The fetus presented with episodes of ventricular ectopy progressing to incessant VT and hydrops fetalis. Genetic analysis disclosed a novel, *de novo* heterozygous mutation in *SCN5A* (L409P) and a homozygous common variant (R558).

Electrocardiographically concealed LQTS (ecLQTS): this term is used to indicate individuals with genotype of LQTS and a phenotype with normal QT interval (corrected QT interval ≤ 440 ms). They are usually detected on family screening of those with manifest LQTS [6]. ecLQTS represents ≈20–40% of all cases of LQTS. The risk of SCD or ACA is ten times higher in those with ecLQTS than the unaffected family members (4% vs four tenths of a percent). This is not withstanding the finding that those with manifest LQTS had a much higher risk of SCD or ACA at 15%. In ecLQTS, the risk of SCD or ACA is higher in those in LQT1 and LQT3 genotypes than in LQT2 genotype [7]. But unlike in manifest LQTS, females were not shown to be at higher risk in concealed LQTS.

Mechanism: The basic defect in LQT3 or LQTS-type-3 - which is the third most common LQTS - is caused by an excessive inflow of late Na^+ current during the plateau, dome or phase 2 of the AP caused by gain-of-function mutations in the SCN5A cardiac Na^+ channel gene which mediates the fast Nav1.5 current during AP initiation and also late in phase 2 of AP causing an accelerated recovery from inactivation of Na^+ current as well as AP prolongation, especially at low stimulation rates. and for improving treatment efficacies. Late inward Na^+ current (I_{Na}). It is an integral part of the Na^+ current, which persists long after the fast-inactivating component: the larger and transient peak I_{Na}. The magnitude of the late I^+_{Na} is relatively small in all species and in all types of cardiomyocytes as compared with the amplitude of the fast Na^+ current of phase 0, but it contributes significantly to the shape and duration of the AP and surface ECG. This late component had been shown to increase in several acquired or congenital conditions, including hypoxia, oxidative stress, and heart failure, or due to mutations in SCN5A, which encodes the α-subunit of the Na^+ channel, as well as in channel-interacting proteins, including four β-subunits and anchoring proteins. Patients with enhanced late I^+_{Na} exhibit the LQT3 variant characterized by high propensity for the life-threatening ventricular arrhythmias, such as TdP, as well as for AF. There are several distinct mechanisms of arrhythmogenesis due to abnormal late INa^+ including abnormal automaticity, induced trigger activity both early and delayed after depolarization (EAD and DAD), and dramatic increase of transmural ventricular dispersion of repolarization. Many local anesthetic and antiarrhythmic agents have a higher potency to block late I_{Na+} as compared with fast. In summary, Na^+ channels open and inactivate rapidly during depolarization (phase 0 of AP) and reopen during the phase 2 plateau/dome phase, carrying 'persistent' or 'late' inward current (late *I*Na). Maltsev et al. found I_{NaL} was activated at a membrane potential of −60 mV with maximum density at −30 mV in cardiomyocytes of both normal and failing hearts. The steady-state availability was sigmoidal, with an averaged midpoint potential of -94 ± 2 mV and a slope factor of 6.9 ± 0.1 mV. The current was reversibly blocked by the Na^+ channel blockers tetrodotoxin and saxitoxin in a dose-dependent manner. Both inactivation and reactivation of I_{NaL} had an ultraslow time course (0.6 s) and were independent of voltage. The amplitude of I_{NaL} was independent of the peak transient Na^+ current.

Malan et al. [8] observed in LQT3 hiPSC models, a high incidence of EADs which is a trigger mechanism for arrhythmia in LQT3. EADs predisposes to ventricular arrhythmias by exaggerating the dispersion of refractoriness throughout the myocardium and increasing the probability of EAD, a phenomenon caused largely by reactivation of calcium channels during the AP plateau. Administration of specific Na^+ channel inhibitors was found to shorten AP durations in a dose-dependent manner. These findings were in full agreement with the pharmacological response profile of the underlying patient and of other patients from the same family. Thus, these observations demonstrate the utility of patient-specific LQT3 hiPSCs for assessing pharmacological responses to putative drugs. Brugada syndrome mutations cause a reduced Na^+ current, while LQT3 mutations are associated with a gain of function (mirror image) consequently these allelic syndromes result from opposite molecular effects. Phenotypic overlap may exist between the BrS and LQT3. Na^+ channel blockade by antiarrhythmic drugs improves the QT interval prolongation in LQT3 but worsens the BrS ST-segment elevation. Although Na^+ channel blockade has been proposed as a treatment for LQT3, flecainide also evokes "Brugada-like" ST-segment elevation in LQT3 patients.

Using noninvasive mapping with electrocardiographic imaging (ECGI) to map the cardiac electrophysiological substrate LQTS patients display regions with steep repolarization dispersion caused by localized AP duration (APD) prolongation. This defines a substrate for reentrant arrhythmias, not detectable by surface ECG. Steeper dispersion in symptomatic patients suggests a possible role for ECG imaging in risk stratification.

Intracellular Ca^{2+} contributes to the regulation of I_{NaL} conducted by NaV1.5 mutants and, during excitation-contraction coupling, elevated intracellular Ca^{2+} suppresses mutant channel I_{NaL} and protects cells from delayed repolarization. This is a plausible explanation for the lower arrhythmia risk in LQT3 subjects during sinus tachycardia.

Iyer et al. present the first direct experimental evidence that Purkinje cells are uniquely sensitive to LQT3 mutations, displaying electrophysiological behavior that is highly pro-arrhythmic. Additionally, abnormalities in Purkinje cell repolarization were reversed with exposure to mexiletine [9].

Mutations in SCN5A gene can originate numerous cardiac Na^+ channelopathies phenotypes (Fig. 1).

2. Clinical presentation

Manifest with syncope, seizures or SCD. In LQT3, majority of

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