Diagnosis, management and therapeutic strategies for congenital long QT syndrome

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ABSTRACT
Congenital long QT syndrome (LQTS) is characterised by heart rate corrected QT interval prolongation and life-threatening arrhythmias, leading to syncope and sudden death. Variations in genes encoding for cardiac ion channels, accessory ion channel subunits or proteins modulating the function of the ion channel have been identified as disease-causing mutations in up to 75% of all LQTS cases. Based on the underlying genetic defect, LQTS has been subdivided into different subtypes. Growing insights into the genetic background and pathophysiology of LQTS has led to the identification of genotype-phenotype relationships for the most common genetic subtypes, the recognition of genetic and non-genetic modifiers of phenotype, optimisation of risk stratification algorithms and the discovery of gene-specific therapies in LQTS. Nevertheless, despite these great advancements in the LQTS field, large gaps in knowledge still exist. For example, up to 25% of LQTS cases still remain genotype elusive, which hampers proper identification of family members at risk, and it is still largely unknown what determines the large variability in disease severity, where even within one family an identical mutation causes malignant arrhythmias in some carriers, while in other carriers, the disease is clinically silent. In this review, we summarise the current evidence available on the diagnosis, clinical management and therapeutic strategies in LQTS. We also discuss new scientific developments and areas of research, which are expected to increase our understanding of the complex genetic architecture in genotype-negative patients, lead to improved risk stratification in asymptomatic mutation carriers and more targeted (gene-specific and even mutation-specific) therapies.

INTRODUCTION
Congenital Long QT Syndrome (LQTS), as the name implies, is characterised by a prolonged QT interval on the ECG, in the absence of structural heart disease and external factors such as a variety of drugs.1–3 LQTS was first described in the 1950s of the previous century, initially in a family with deafness (ie, Jervell and Lange-Nielsen syndrome). A few years later, in the early 1960s, patients with a similar ECG abnormality but without deafness were described (ie, Romano-Ward syndrome). Although initially this disease was subdivided into these two entities, later in time the more general terminology LQTS was used, and more recently (1995–1996), it became clear that, based on the underlying genetic defect, a further subdivision into distinct subtypes is pertinent. The various milestones in the over 60 years history of this disease are nicely summarised in a recent personal review by Dr Schwartz.4

Genotyping and genotype-phenotype correlations
In the last 25 years, 17 genes have been associated with LQTS. However, a recent analysis, based on an approach using gene and disease specific metrics designed by the Clinical Genome Resource (ClinGen), reclassified a number of these genes to limited or disputed evidence.11 This approach left seven genes with definitive or strong evidence for causality (table 1).11 These remaining genes all encode for ion channels involved in cardiac repolarisation, their modulatory subunits or proteins regulating or modulating the function of ion channels. A positive genotype result, which is obtained in up to 75% of individuals with a clear phenotype, is of importance because it significantly contributes to risk and different aspects of the treatment strategy.2,3

Indeed, specific genotype-phenotype relationships have been described for the three most common subtypes: LQTS types 1, 2 and 3 (figure 3).
The first two subtypes (LQT1 and 2) are based on functional loss-of-function variants in the potassium channel genes KCNQ1 and KCNH2, respectively. These genes respectively encode for the slow and rapid delayed rectifier current $I_{Ks}$ and $I_{Kr}$, and a smaller amplitude of this current leads to prolongation of the QT interval (figure 4A–D). LQTS type 3 is based on gain-of-function variants in SCN5A, the gene encoding the fast inward cardiac sodium current ($I_{Na}$). Gain of function relates to an increased amplitude of the late sodium inward current (during the plateau phase), which will also lead to prolongation of the action potential (figure 4D).

The age of onset of arrhythmias is typically younger in LQT1 patients and in particular LQT1 males are at risk, whereas most LQT2 and LQT3 patients who become symptomatic experience their first symptoms around puberty and here particular females are at risk (figure 3). Also, the morphology of the ST-T segments is rather specific for the three subtypes, and the genotype can be accurately predicted with these characteristic features.1213 Furthermore, each genotype also has specific triggers for arrhythmic events and rather specific electrocardiographic features of the onset of the arrhythmias (figure 3).14–16 The arrhythmias in LQTS (figure 4F) originate from the last part of the ventricular action potential where severe action potential prolongation results in early afterdepolarisations that at one instant reach threshold for subsequent fast sodium inward current and a trigger beat that then degenerates into fast
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polymorphic ventricular arrhythmia: Torsades de Pointes and ventricular fibrillation. Adrenergic triggers, particularly exercise and swimming, are the most important trigger for arrhythmic events in LQT1, whereas in LQT2 sudden arousal (ie, auditory stimuli) is predominant (figure 3). Events in LQT3 occur most frequently in rest. These gene-specific characteristics not surprisingly associate with a high response to β-blockers of LQT1 patients, although also in LQT2 and LQT3 patients β-blockers constitute the first line of therapy. LQT3 patients are most sensitive to (late) sodium channel current blockers. Because of the genotype-specific features (figure 3) with impact on prognosis and therapy, genetic testing has become an integral part of the diagnosis and management of LQTS patients.

**Clinical management and treatment strategies**

As indicated, the cornerstone of management of LQTS patients is β-blocker therapy (figure 5). The non-selective β-blockers nadolol and propranolol have been advocated as the most effective drugs. The efficacy of propranolol was questioned, but we believe that the published data from the LQTS registry are ‘contaminated’ with the inclusion of symptomatic newborns, which is a severe condition with failure of almost every therapeutic attempt. This includes propranolol, the only available β-blocker in liquid form and therefore exclusively given in this patient group. Metoprolol and atenolol are less effective and should be avoided, at least in symptomatic patients. The anti-arrhythmic effect of β-blockers is due to the prevention of early after depolarisations by blocking the adrenergic driven boost of calcium current. Only propranolol reduces the QTc to some extent by blocking late sodium inward current. There is no doubt that all symptomatic patients should be treated. However, although we have shown that active treatment is installed in the vast majority of presymptomatically screened individuals, the need for treatment in asymptomatic individuals is less determined (see further). This is not a trivial issue because the latter group expands rapidly with active cardiogenetic programmes.

Additional pharmacological therapy consists of blockers of the late sodium inward current (ie, mexiletine, flecainide and ranolazine). As mentioned previously, LQT3 patients in particular are responsive to sodium channel blockers, but in a recent study, mexiletine has also been shown to reduce the QTc in LQT2 patients. Sodium channel blockers, which also block
the fast sodium inward current, may, while shortening QTc, provoke a Brugada ECG pattern however, which thus warrants evaluation.25 The latter is particularly relevant in patients with SCN5A variants with both gain-of-function and loss-of-function characteristics.26 Potassium suppletion has been shown to be particularly effective in LQT2 because the conductance slope of $I_{K1}$, the affected current in LQT2, heavily depends on the extracellular potassium level (the higher, the steeper).27 28 Still, also the $I_{Kr}$ and $I_{Ks}$ currents are critically dependent on extracellular potassium levels29 30 and may thus well contribute to increased QTc intervals and an increased risk for arrhythmia in states of low plasma potassium levels.

New pharmacological therapy is emerging, but the target population becomes more and more specific. In patients with KCNH2 trafficking defects (ie, mutated protein products that do not travel adequately to the cell membrane), lumacaftor has been shown to shorten the QTc significantly.31 Lumacaftor is a potassium rectifier currents during phase 3 and phase 4 (I_{Ks}, I_{K1}) are critically dependent on extracellular potassium levels29 30 and may thus well contribute to increased QTc intervals and an increased risk for arrhythmia in states of low plasma potassium levels.

The next level of therapy is left cardiac sympathetic denervation (LCSD). β-blocker breakthrough events are not rare, and additional therapy is thus frequently required. LCSD is the first choice in β-blocker resistant patients (figure 5).3 33 34 Indeed, the HRS/EHRA/APHRS expert consensus has recommended for LCSD to be performed in high-risk patients with a diagnosis of LQTS in whom: (1) ICD therapy is contraindicated or refused and/or (2) β-blockers are either not effective in preventing syncope/arrhythmias, not tolerated, not accepted or contraindicated (class I), and it may be useful in patients with a diagnosis of LQTS who experience breakthrough events while on therapy with β-blockers/ICD (class IIa). LCSD is particular effective in LQT1 patients, but also LQT2, LQT3, gene-elusive LQTS and patients with multiple mutations (eg, compound heterozygous) may respond well on LCSD.3 35

Device therapy is the final level of therapy in LQT patients with β-blocker and/or LCSD breakthrough cardiac events or in patients with an anticipated high risk for arrhythmic events. In patients who survived a cardiac arrest, ICDs have a class 1 recommendation (on top of β-blockers; figure 5), with a possible exception of LQT1 patients who were not yet diagnosed (and, as a consequence, not treated with β-blockers) at the time of...
their arrest. ICDs are well accepted and have shown clear benefit in primary and secondary sudden cardiac death prevention. However, ICD therapy does not come without disadvantages. In a systematic review with an emphasis on ‘ICD-harm’ in patients with inherited arrhythmia syndromes, the yearly rate of complications in LQT patients was 7.0% (95% CI 4.4 to 9.7) on top of a yearly 3% of inappropriate shocks (2.0–3.6).36 Appropriate therapy was 1.9% and 6.8% in, respectively, primary and secondary prevention patients.36

Pacemaker therapy has not extensively been tested in LQTS but may be beneficial in particular in LQT2 patients where arrhythmias are almost exclusively pause dependent.16 Likewise, pause-dependent algorithms (‘rate smoothing’) have successfully been applied in single cases.37 In LQT3, QTc prolongation is particularly evident at lower rates, so also in this subentity, background pacing at a higher than spontaneous rate, which is actually low in LQTS patients, may be beneficial. The latter has been well shown in a large family with a specific LQT3 variant.26

Figure 5  Schematic flow chart for the therapeutic choices in LQTS. Flow chart for therapeutic choices in LQTS following the HRS/EHRA/APHRS consensus document from 2013.3 See text for further discussion. ICD, internal cardioverter defibrillator; LQTS, long QT syndrome.

Figure 6  Schematic representation of the effects of genetic and environmental factors in LQTS. (A) LQTS-associated mutation causes prolongation of the QT interval on the ECG. (B) Environmental factors such as certain drugs (which decrease repolarisation reserve) or hypokalaemia, or genetic factors (ie, deleterious alleles) act in a conjoint manner with the LQTS-associated mutation to further prolong the QT interval. (C) Protective alleles counteract the effects of the mutation and reduce the extent of QT prolongation. The presence of deleterious and/or protective alleles may underlie, at least partially, the variable expressivity in LQTS. LQTS, long QT syndrome.
Furthermore, in the rare but severe Jervell Lange-Nielsen type LQTS, atrial pacing has been shown to be very effective already at young age. Pacing at a higher rate (>100/min) has also been shown to be temporarily effective, by preventing pauses, in the acute phase of an arrhythmic storm.

Knowledge gaps or future research opportunities
The advancement of knowledge in the LQTS field has been tremendous with the change from the description of individuals with an electrocardiographic curiosity, many of whom died suddenly, to a genotype-specific approach of the different disease subtypes. This development has led to more sophisticated risk stratification, genotype-specific treatment modalities and significantly reduced mortality. However, further optimisation of treatment strategies is pertinent, in particular in two specific patient categories. The first is a small group of treatment resistant severe LQTS, most often consisting of neonates with specific SCN5A mutations (eg, R1623Q), CALM mutations, or Triadin mutations, or patients with double mutations. These patients not rarely die despite aggressive treatment on all levels, including ICDs. New, more effective drugs are needed for this small subgroup. The second group is much larger and still expanding because of the proactive cardiogenetic counselling programmes around the world. Many of these symptomatic counselled individuals have a normal or only marginally prolonged QTc and one may question whether they do need treatment and strict preventive measures at all. More sophisticated risk stratification in this group of patients is desperately needed.

Furthermore, and relevant for all patients, it is important to note that adherence to β-blocker therapy is overall poor. In a study from New Zealand, adequate adherence was reported on all levels, including ICDs. New, more effective drugs are needed for this small subgroup. The second group is much larger and still expanding because of the proactive cardiogenetic counselling programmes around the world. Many of these symptomatic counselled individuals have a normal or only marginally prolonged QTc and one may question whether they do need treatment and strict preventive measures at all. More sophisticated risk stratification in this group of patients is desperately needed.

Finally, despite all progress in genetic screening methods, the yield of finding a potential pathogenic variant in a LQTS patient with a clear phenotype is at most 75%–80%. However, in dedicated cardiogenetic clinics the yield was lower, around 50%, with these higher values only in earlier years and lower values in more recent years because of a more lenient case selection in recent years. Important additional scientific inquiries in this field are the unravelling of the genotype in the 25%–30%genotype elusive cases and the role of additional genetic and other factors in determining the arrhythmia risk. For example, comorbidities like hypertension may aggravate the LQTS phenotype by deleterious effects of the interaction between hypertrophy and the mutation. Furthermore, recent data show evidence for a more complex polygenic architecture in genotype-negative patients, and preliminary evidence in single families has revealed evidence for the existence of both protective as well as deleterious alleles, which may modify the phenotype by, respectively, aggravating (figure 6B) or alleviating (figure 6C) the QT-prolonging effects of a LQTS-causing mutation. New genes, yet to be identified, may also form a partial explanation for the genetic underpinning in gene-elusive patients.

In summary, congenital LQTS is an inheritable entity characterised by a prolonged heart-rate corrected QT interval, and it associates with malignant arrhythmias at young age. It is caused by a decrease in repolarising cardiac ion currents in a complex polygenic composition and interacting with multiple other factors such as sex, age, comorbidities and triggers such as drugs. Therapy relies importantly on β-blockers and lifestyle measures. More patient specific pharmacological and invasive therapies are available and under continuous development. A better understanding of its complex architecture paves the path to improving care for these patients and their families.

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