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Pharmacological and Non-Pharmacological Management of the Congenital Long QT Syndrome: The Rationale

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Abstract

The congenital long QT syndrome (LQTS) is a familial disorder characterized by a prolongation of the QT interval on the ECG and occurrence of life-threatening cardiac arrhythmias especially, but not only, under conditions of increased sympathetic activity. Symptomatic untreated patients are at high risk for sudden cardiac death. Twelve LQTS genes have been identified and most of them encode cardiac ion channels. Very effective therapies are available and in carefully treated patients mortality is around 0.5–1% over 20 years.

The initial treatment should always involve β -blockers, with propranolol and nadolol being the two most effective ones. With few exceptions all mutation carriers should be treated because of the risk of sudden death during the first cardiac event. Approximately 20% of patients continue to have syncope despite β -blockers and the most rationale next level of therapy is represented by Left Cardiac Sympathetic Denervation (LCSD), which is highly effective and can complement any other therapy. One important limitation of LCSD is that, without valid reasons, it is available only in a few selected centers. Whenever syncope recurs despite LCSD, or whenever an aborted cardiac arrest has occurred, it becomes logical to resort to the implantation of a cardioverter defibrillator (ICD). The latter, however, are burdened by a high rate (31%) of adverse events including severe ones such as endocarditis, inappropriate shocks, and by the need of frequent battery replacements. A scoring system, based on simple clinical variables, can identify the patients more and less likely to benefit from ICD implantation.

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Keywords

Long QT syndrome; Sudden cardiac death; Genetics; Left cardiac sympathetic denervation; β -adrenergic blocking agents; Implantable cardioverter defibrillators

INTRODUCTION

The congenital long QT syndrome (LQTS) is a relatively uncommon but important clinical disorder of genetic origin. Since 1975 (Schwartz et al., 1975), under the unifying name of the "Long QT Syndrome" it includes two hereditary variants. The Jervell and Lange-Nielsen syndrome (J-LN) is associated with deafness (Jervell and Lange-Nielsen, 1957; Schwartz et al., 2006) and the Romano-Ward syndrome (R-W) is not (Romano et al., 1963; Ward, 1964).

The interest for LQTS has progressively increased, reaching an almost exponential growth during the last 15 years. The reasons are multiple, including two which are not novel. One is represented by the dramatic manifestations of the disease, namely syncopal episodes which often result in cardiac arrest and sudden death and usually occur in conditions of either physical or emotional stress in otherwise healthy young individuals, mostly children and teenagers. Another is that, while LQTS is a disease with a very high mortality rate among untreated patients, very effective therapies are available; this makes unacceptable and inexcusable the existence of symptomatic and undiagnosed or misdiagnosed patients. Since 1995 the identification of several genes responsible for LQTS, and moreover the realization that so far most of them encode ion channels, has provided a new stimulus for clinical cardiologists and basic scientists. The impressive correlation between specific mutations and critical alterations in the ionic control of ventricular repolarization makes this syndrome a unique paradigm which allows to correlate genotype and phenotype, thus providing a direct bridge between molecular biology and clinical cardiology in the area of sudden cardiac death.

Here, I will focus primarily on therapy. As generalities go, details on clinical manifestations can be found in a recent review (Schwartz and Crotti, 2009), the prevalence of LQTS is close to 1/2,000 live births based on a prospective ECG study complemented by molecular screening in 44,000 infants (Schwartz et al., 2009a), and even though 12 LQTS genes have been identified the most important remain the first 3 identified which encode the I_{Ks} , the I_{Kr} , and the I_{Na} current (Schwartz and Crotti, 2009; Schwartz, in press).

MANAGEMENT AND THERAPY FOR LQTS

The cardinal aspects of LQTS therapy and management are essentially four: the two types of antiadrenergic interventions (β -blockers and left cardiac sympathetic denervation, LCSD), the implantable cardioverter defibrillator (ICD), and gene-specific management, which is still in its infancy.

Antiadrenergic Interventions

The most significant information on therapy still comes from the 1985 study (Schwartz and Locati, 1985) which included 233 symptomatic patients with detailed clinical information on the time of first syncope and with an adequate follow-up. The mortality at 15 years after the first syncope was 9% in the group treated by antiadrenergic therapy (β -blockers and/or sympathectomy), and more than 53% in the group not treated or treated by miscellaneous therapies not including β -blockers (Fig. 1). These data conclusively demonstrated that pharmacological and/or surgical antiadrenergic therapy radically modifies prognosis for symptomatic patients with LQTS. In 2009 the mortality for patients treated with β -blockers

and LCSD has dropped to around 1%. The dramatic success of carefully executed therapies is a stark warning about the unacceptability of LQTS symptomatic patients either undiagnosed or incorrectly treated.

β -Blockers— β -adrenergic blocking agents represent the first choice therapy in symptomatic LQTS patients, unless specific contraindications are present.

Propranolol and nadolol are the two most effective drugs. Their respective dosages are 3 mg/kg, sometime increased to 4 mg/kg, and 1 mg/Kg. The main advantages of propranolol are its lipophilicity, that allows it to cross the blood-brain barrier, and its well known tolerability for chronic therapy; its main disadvantages are the need of multiple daily administrations and the contraindications for patients with asthma and diabetes. We more and more often use nadolol, as its longer half-life allows twice a day administration. This increases compliance, particularly when dealing with teenagers who may easily forget to take their medication in the afternoon. Unfortunately, β -blockers are not “all Indians of the same tribe” and many of them are unquestionably less effective; this group includes bisoprolol, metoprolol, atenolol, and carvedilol. The high efficacy of propranolol is often explained on the basis of its complementary sodium channel blocking activity but this explanation makes even more intriguing the equal efficacy of nadolol which affects neither the peak Na current nor its delayed component (A. Besana et al, manuscript in preparation).

In a large number of patients of unknown genotype, mortality on β -blocker therapy was 2%, and it was 1.6% when limited to patients with syncope (no cardiac arrest, CA) and without events in the first year of life (Moss et al., 2000). There is clear evidence that β -blockers are extremely effective in LQT1 patients. Data from two large studies (Schwartz et al., 2001; Priori et al., 2004) indicated that mortality is around 0.5%, and sudden death combined with cardiac arrest reaches 1%. The impairment in the I_{Ks} current makes these patients particularly sensitive to catecholamines and quite responsive to β -blockade. These patients seldom need more than antiadrenergic therapy.

Particularly, important information has come from a study published in 2009 (Vincent et al., 2009). Vincent et al performed a retrospective study of the details surrounding cardiac events in 216 genotyped LQT1 patients treated with β -blockers and followed for 10 years. Before β -blocker therapy, cardiac events occurred in 157 patients (73%) at a median age of 9 years, with CA in 26 (12%). After β -blockers, 75% were asymptomatic, and the risk for life-threatening cardiac events was reduced by 97% ($p < 0.001$). Twelve patients (5.5%) suffered CA/sudden death, but 11 of 12 (92%) were either noncompliant ($n=8$), on a QT-prolonging drug ($n=2$), or both ($n=1$) at the time of the event. The only compliant patient who died was a child affected by the very malignant J-LN syndrome (Schwartz et al., 2006).

The risk for CA/sudden death in compliant patients not taking QT-prolonging drugs was dramatically less compared with noncompliant patients on QT-prolonging drugs (odds ratio, 0.03; 95% C.I. 0.003 to 0.22; $p < 0.001$). None of the 26 patients with CA before β -blocker had CA/sudden death on β -blockers. The conclusion was that β -blockers are extremely effective in LQT1. β -blocker noncompliance and use of QT-prolonging drug are responsible for almost all life-threatening “ β -blocker failures.”

Partly because of the small numbers available (which affect percentages), a concept unsupported by any firm evidence has rapidly spread; namely, that LQT3 patients are not protected at all by β -blockers or by anti-adrenergic therapy. As a matter of fact, actual data point to a profound difference in the response to therapy for these patients based on the age of the first manifestation. If cardiac events occur during the first year of life, then β -blockers are insufficient and the disease has a very malignant course. On the other hand, with a mean

follow-up of 9 years, LQT3 patients without cardiac events in the first year of life have done extremely well with β -blockers and/or LCSD (Schwartz et al., 2009b). A large study on more than 300 LQT3 patients is now supporting this concept (A.Wilde et al, manuscript in preparation), but the evidence already available indicates that a molecular diagnosis of LQT3 in an asymptomatic patient should never lead to an automatic decision to implant an ICD.

Left Cardiac Sympathetic Denervation—A thorough description of LCSD has just been published (Odero et al., 2010). Following a small incision in the left subclavicular region, LCSD is performed by an extrapleural approach which makes thoracotomy unnecessary. The average time for surgery is 35–40 minutes. LCSD requires removal of the first four thoracic ganglia. The cephalic portion of the left stellate ganglion is left intact to avoid the Horner's syndrome. In 25–30% of patients there is a very modest (1–2 mm) ptosis which can be noted only by close examination but fully escapes notice in normal social interactions. There is also growing interest for a thoracoscopic approach (Atallah et al., 2008; Collura et al.; 2009; Schwartz, 2009).

The rationale for the use of LCSD lies in the vast experimental experience which has demonstrated its powerful antifibrillatory effect in ischemic and non-ischemic conditions (Schwartz and Malliani, 1975; Schwartz et al., 1976; Schwartz, 1984; Schwartz, 2009; Schwartz, 2010a).

The latest worldwide data published in 2004 include 147 LQTS patients who underwent LCSD during the last 35 years (Schwartz et al., 1992). They represented a very high risk group, as 99% were symptomatic, as their mean QTc was very long (563 ± 65 ms), as 48% had a cardiac arrest and especially as 75% continued to have syncope despite full-dose β -blockers. The data most relevant to current clinical decisions are those regarding patients without cardiac arrest (who almost always should receive an ICD) and who suffer syncope despite being treated with a full dose of β -blockers. During a mean follow-up of 8 years there was a 91% reduction in cardiac events. LCSD produced a mean QTc shortening of 39 ms, pointing to an action on the substrate as well as on the trigger. Mortality was 3% in this high risk group. A post-surgery QTc < 500 ms predicted a very favorable outcome (Fig. 2). Importantly, this series included 5 patients who underwent LCSD due to multiple ICD shocks and electrical storms: in this group, over a 4-year follow-up there was a 95% decrease in the number of shocks (from an average of 29 shocks/year) with a dramatic improvement in the quality of life of the patients and of their families. A new assessment of the long term results with LCSD is underway and will involve most of the patients operated all over the world.

The major antifibrillatory efficacy of LCSD has been previously demonstrated in high-risk postmyocardial infarction patients (Wilde et al., 2008), and recently in patients with catecholaminergic polymorphic ventricular tachycardia (CPVT) not protected by β -blockers and receiving multiple appropriate shocks by the ICD (Wilde et al., 2008). The Boston Children Hospital and the Mayo Clinic have recently published their successful experience with LCSD in both LQTS and CPVT (Atallah et al., 2008; Collura et al.; 2009; Schwartz, 2009).

Whenever syncopal episodes recur despite a full-dose β -blocking therapy, LCSD should be considered and implemented whenever possible. It is unfortunate that, despite its relative simplicity, LCSD is not performed in many high risk patients because cardiovascular surgeons are no longer familiar with the procedure. The consequence is that too often the choice goes to the easiest approach, namely an ICD, even when this choice is not the best for the patient. Before making a therapeutic decision for a young patient with syncope despite β -

blockers, the patients and their families have the right to be informed about the long terms benefits and limitations of both LCSD and ICD. Failure to provide fair information on both these options may carry medico-legal consequences (Schwartz, 2010b).

Implantable Cardioverter Defibrillators

There has been a major increase, largely unjustified, in the number of ICDs implanted in LQTS patients. There is a consensus for immediately implanting an ICD in case of a documented cardiac arrest, either on or off therapy, unless the event appears due to a transient and reversible cause. By contrast, opinions differ strongly regarding the use of ICDs in patients without cardiac arrest.

The US (Zareba et al., 2003) and the European (Schwartz et al., 2010) ICD-LQTS Registries provide the disquieting information that the majority of implanted patients had not suffered a cardiac arrest and, moreover, that many had not even failed β -blocker therapy. A recent multicenter study went as far as indicating that the mere presence of a *SCN5A* mutation, even in a totally asymptomatic individual, is sufficient for immediate ICD implant (Etheridge et al., 2007).

It should not be forgotten that ICDs do not prevent occurrence of malignant arrhythmias and that Torsades-des-Pointes ventricular tachycardias (TdP) are frequently self-terminating in LQTS. The recurrence of electrical storms has led to suicidal attempts in teenagers and its high incidence (>10%) in children has been considered by a large group of experienced pediatric cardiologists as “devastating” (Wolf et al., 2007). The massive release of catecholamines, triggered by pain and fear, that follows an ICD discharge in a conscious patient – especially a young one – leads to further arrhythmias and to further discharges which produce a dramatic vicious circle.

Special caution is necessary before choosing to implant an ICD in a child with LQTS. Such a decision is seldom justified before a proper trial with combined antiadrenergic therapy, i.e. full-dose β -blockade and LCSD, which prevents sudden death in 97–98% of symptomatic and high-risk patients, and which still allow an ICD implant in case of a new syncope or cardiac arrest. On the other hand, the nature of the disease is such that cardiac arrests may recur and have lethal consequences. Thus, concerns for the life of the patients and the interference of medico-legal considerations represent a reality. The risk-benefit ratio of an ICD should be clearly explained to the patient or to his/her parents together with information on the pro and cons of LCSD, to allow them the possibility of a choice.

Very recently, the largest-to-date experience on ICDs in LQTS has been published (Schwartz et al., 2010). These European data on 233 LQTS patients with an ICD (28) indicate that 9% of patients were asymptomatic and that 41% received an ICD without having been placed first on LQTS therapy. Within 5 years, 31% of the patients suffered adverse events. Appropriate ICD discharges occurred in 28% of patients and could be predicted by a specifically developed scoring system.

The development of this scoring system (M-FACT) to predict the probability of appropriate therapies from the ICD deserves a specific mention because of its practical implications. We wanted to provide clinicians with the possibility of identifying early on those patients expected to benefit most from ICD implantation and also those less likely to receive appropriate shocks once treated with β -blockers. Accordingly, we focused on clinical variables immediately available in a doctor's office; for this reason we did not consider genotype because most of the time the decision of implanting an ICD arises for patients not yet genotyped and genotyping takes several months. Following a univariate analysis, a multivariate Cox model identified 4 variables (age <20 at implant, QTc > 500 ms, prior

cardiac arrest, and cardiac events despite therapy) as independent predictors of future appropriate shocks, allowing their combination and the development of an M-FACT score based on the number of these risk factors when coexisting in the same patient (Table 1).

Figure 3A shows that in the entire population the 7-year cumulative survival to a first appropriate shock decreased from 100% for patients with no risk factors to 30% for patients with ≥ 4 point score, with a progressively lower probability of escaping shocks according to the increasing number of risk factors ($P < 0.001$). Figure 3B shows that when the same analysis was performed after exclusion of the patients with a prior ACA (because the difficult decisions concern the patients without an ACA), the pattern remained essentially the same. In low-risk patients (score 0 to 1), the 7-year cumulative survival to first appropriate shock for the 2 subsets was 88% (95% CI, 78 to 94) and 97% (95% CI, 87 to 99). Among patients without the 4 risk factors no one received appropriate shocks within 7 years, in contrast to 70% of those with all four factors.

Patients with an M-FACT score of 0 should receive an ICD only on the basis of very cogent, patient-specific arguments. For them, the odds are not in favor of benefit from the ICD. We believe that with careful programming (e.g., using only the VF zone at high rate, with a long time for tachycardia detection and perhaps antibradycardia pacing), it might be possible to reduce the number of both inappropriate shocks and appropriate but not necessary shocks, with significant benefits for the quality of life of these patients.

Our current policy is to implant an ICD after a cardiac arrest with the exception of reversible/transient triggers, always when firmly requested by the patient, when syncope recurs despite β -blockade and LCSD, in the subgroups identified as “at high risk” by the M-FACT score, and whenever our clinical sense detects imminent danger despite therapy.

Gene-Specific Therapy and Management

Gene-specific therapy for LQTS is still in its infancy. On the other hand, the realization that there are gene-specific triggers for cardiac events has led to a series of directions for management that on one hand are indeed gene-specific and on the other can significantly decrease risk for the affected patients.

LQT1 patients are at higher risk during sympathetic activation, such as during exercise and emotions. They should not participate in competitive sports. Swimming is particularly dangerous, as 99% of the arrhythmic episodes associated with swimming occur in LQT1 patients (Schwartz et al., 2001).

In LQT2 patients, some of whom have a tendency to lose potassium, it is essential to preserve adequate potassium levels. Oral K^+ supplements in combination with K^+ sparing agents are a reasonable approach. As these patients are at higher risk especially when aroused from sleep or rest by a sudden noise (Schwartz et al., 2001), we recommend that telephones and alarm clocks are removed from their bedrooms and, especially with children, whenever they have to be wakened up in the morning, to do it gently and without yelling.

The realization that *SCN5A* mutations producing LQT3 have a “gain-of-function” effect (Bennett et al., 1995) has lent support to our early suggestion (Schwartz et al., 1995) to test sodium channel blockers, and especially mexiletine, as possible adjuvants in the management of LQT3 patients (Schwartz, 2006). We test the effectiveness of mexiletine in all LQT3 patients by the acute oral drug test technique (half the daily dose during continuous ECG monitoring). Within 90 minutes the peak plasma concentration is reached and if the QTc is shortened by more than 40 ms then we add mexiletine to the β -blocker therapy. As a matter of fact, in 2/3 of LQT3 patients mexiletine shortens QTc by more than

70–80 ms (Fig. 4). Even though there is no conclusive evidence for a beneficial effect and definite failures have occurred, there is also growing evidence of significant benefit in a number of individual cases. There are highly malignant forms manifesting in infancy due to mutations causing extremely severe electrophysiological dysfunction corrected by the combination of mexiletine and propranolol (Wang et al., 2008).

During heart rate increases QTc shortens more in LQT3 patients than among healthy controls (32) and indeed normal physical activity may not need to be restricted in LQT3 patients. They are at higher risk of death at rest and especially nighttime. When these patients sleep, and are in a horizontal position, the onset of TdP produces a progressive but slow fall in blood pressure that facilitates a noisy gasping preceding death. This has led both LQT2 (also at risk while resting) and LQT3 patients to be saved by a family member, such as the spouse sleeping in the same bed. Accordingly, we recommend that LQT2 and LQT3 patients have an intercom system in their and – if young – in their parents bedrooms.

Various research groups, including ours, are working on sophisticated approaches to gene-specific therapy, including RNA silencing for gain-of-function mutations. For example, the development of an RNA silencer (siRNA) expression, mediated by an adeno-associated virus vector, would have the aim of silencing the pathological allele responsible for LQT3. However, it will be a while before these novel approaches will impact on clinical management.

OVERVIEW ON THERAPY

The clear data available, and decades of clinical experience, dictate the therapeutic approach to the patient affected by LQTS who already has had a syncopal episode. Treatment should always begin with β -blockers, unless there are valid contraindications. If the patient has one more syncope despite full dose β -blockade, LCSD should be performed without hesitation and ICD implant should be considered with the final decision being based on the individual patient characteristics (age, sex, previous history, genetic subgroup including sometime mutation-specific features, presence of ECG signs – including 24-hour Holter recordings - indicating high electrical instability). In the end, when our objective is to protect the patients from lethal arrhythmias and at the same time to ensure their quality of life, there is no substitute for careful clinical judgment accompanied by a thorough knowledge of the several variants of this unique life-threatening cardiac disorder.

LIST OF ABBREVIATIONS

ACA	Aborted Cardiac Arrest
CA	Cardiac Arrest
CPVT	Catecholaminergic Polymorphic Ventricular Tachycardia
ICD	Implantable Cardioverter Defibrillator
LCSD	Left Cardiac Sympathetic Denervation
LQTS	Long QT Syndrome
TdP	Torsade de Pointes

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Figure 1.

Effect of therapy on the survival, after the first syncopal episode, of 233 patients affected by the congenital LQTS. The protective effect of β -adrenergic blockade and of left stellectomy (LSGx) is evident. The mortality 3 years after the first syncope is 6% in the group treated with antiadrenergic interventions and 26% in the group treated differently or not treated. Fifteen years after the first syncope, the respective mortality rates are 9% and 53%. (From Schwartz and Locati, 1985)

Figure 2. Kaplan-Meier curves of event-free survival and survival according to QTc interval after left cardiac sympathetic denervation in patients with only syncope, or aborted cardiac arrest before left cardiac sympathetic denervation. (*Modified from Schwartz et al., 2004*).

Figure 3. Cumulative event-free survival for a first appropriate ICD shock according to an increasing risk score in (A) all patients and (B) in patients with no prior ACA. (From Schwartz *et al.*, 2010)

Figure 4. LQT3 patient aged 17-years, major QTc prolongation (QTc 516 ms) not modified by β -blocker therapy. The addition of oral chronic therapy with mexiletine (200 mg b.i.d.) produced a major shortening of QTc by over 100 ms persisting over time. (From Schwartz *et al.*, 2006)

Table 1**M-FACT * RISK SCORE**

	- 1 point	0 points	1 point	2 points
Event free on therapy for > 10 yrs	Yes			
QTc (ms)		≤ 500	> 500 – ≤ 550	> 550
Prior ACA		No	Yes	
Events on therapy		No	Yes	
Age at implant		> 20 yrs	≤ 20 yrs	

* Acronym derived from **M** (Minus 1 point for being free of cardiac events while on therapy for >10 years); **F** (“Five Hundred” and “Five hundred and Fifty ms QTc); **A** for Age ≤ 20> years at implant; **C** (Cardiac arrest); **T** (events on Therapy).

ACA = Aborted Cardiac Arrest
(From Schwartz *et al.*, 2010)