Clinical update

The long QT syndrome: a transatlantic clinical approach to diagnosis and therapy

Peter J. Schwartz1,2,3,4,5* and Michael J. Ackerman6,7,8

1Department of Molecular Medicine, University of Pavia, Pavia, Italy; 2Department of Cardiology, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy; 3Cardiovascular Genetics Laboratory, Department of Medicine, Hatter Institute for Cardiovascular Research in Africa, University of Cape Town, Cape Town, South Africa; 4Department of Medicine, University of Stellenbosch, Stellenbosch, South Africa; 5Chair of Sudden Death, Department of Family and Community Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia; 6Department of Medicine, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA; 7Department of Pediatrics, Division of Pediatric Cardiology, Mayo Clinic, Rochester, MN, USA; and 8Department of Molecular Pharmacology & Experimental Therapeutic, Windland Smith Rice Sudden Death Genomics Laboratory, Mayo Clinic, Rochester, MN, USA

Received 5 December 2012; revised 31 January 2013; accepted 31 January 2013; online publish-ahead-of-print 18 March 2013

The mind-boggling progress in understanding the molecular mechanisms underlying the long QT syndrome (LQTS) has been the subject of many articles and reviews. Still, when it comes to the management of the patients affected by this life-threatening disorder, too many errors still take place, both in the diagnostic process and in the therapeutic choices. The price of these errors is paid by the patients and their families. This review is not directed to the relatively small number of LQTS experts who know what to do. It does not deal with genetics, with epidemiology, or with the well-known clinical manifestations. We have focused solely on the approach to diagnosis and therapy and we have directed this review to the average clinical cardiologist who, in his/her practice, sees occasionally patients affected or suspected to be affected by LQTS; the cardiologist who may know enough to manage them but not enough to be completely confident on his/her most critical choices. We have provided our personal views without making any attempt to blend differences whenever present. On most issues we agree fully but where we do not, we make it clear to the reader by indicating who is thinking what. The result may be unconventional, but it mirrors the challenges, often severe, that we all face in managing and protecting these patients from sudden death while also helping them live and thrive despite their diagnosis. We trust that this unabashed presentation of our clinical approach will be useful for both cardiologists and patients.

Keywords Long QT syndrome • Sudden cardiac death • Left cardiac sympathetic denervation • Implantable cardioverter defibrillator • QT interval • Genetics

Introduction

A lot has been written about the long QT syndrome (LQTS) and there is a wealth of traditional reviews—from the earliest1,2 to the most recent ones3–5—summarizing the existing knowledge on epidemiology, pathogenesis, clinical presentation, and state of genetic testing. Here, we wanted to offer an unabashed vision on how the two of us, in Europe and in the USA, approach diagnosis and therapy in the patients referred to us daily for suspected or established LQTS. We are not writing for the scientists investigating the intriguing facets of LQTS but for the clinical cardiologist who, from time to time, may happen either to take care of a patient with LQTS or to suspect that he/she may be dealing with one. On most issues, we share a similar view and approach. However, when either our opinions differ or only one of us recommends/follows a certain approach, this will be indicated by listing just one set of initials (P.J.S. or M.J.A.). Hopefully, this review will help to reduce both diagnostic and therapeutic errors and to provide a more consistent and effective management for patients with LQTS.

Diagnostic approaches

As one approaches a patient with the question of LQTS’ presence, it is critical to keep the pre-test probability and index of suspicion squarely in focus as the various diagnostic tests are being contem-
plated, ordered, and then interpreted. Losing sight of this is one of the primary reasons for the observed overdiagnosis of LQTS. Instead, the following methodical, detective-like approach can minimize these diagnostic mishaps.

First, keep in mind that the pre-test probability for LQTS before examining an index case, obtaining their personal and family history, and before staring at their 12-lead electrocardiograms (ECGs), is about 1 in 2000 chance. In contrast, the pre-test probability for a relative where LQTS is already a clinically established and genetically confirmed diagnosis can be as high as 50%.

Secondly, the patient’s story (personal and family history) should be one of the strongest factors that drives the clinical index of suspicion and increases this background likelihood for disease. Here, approximately half of the patients with LQTS have experienced or will experience at least one LQTS-triggered episode of syncope, syncope with seizures, or aborted cardiac arrest (ACA)/sudden cardiac death (SCD). Further, an episode of LQTS-triggered syncope secondary to Torsades des Points ventricular tachycardia is one of the strongest clinical determinants for not only a future faint but also a future ACA/SCD. As such, a meticulous interrogation of each and every spell is necessary to determine and decide whether it ‘sounded’ arrhythmic in origin. Importantly, patients with LQTS also have vaso-vagal-mediated (neurocardiogenic) syncope at the same rate as the general population. Vaso-vagal fainting should not be used to advance the patient’s pre-test probability. In fact, the combined phenotype of a vaso-vagal faint in a patient who then went on to exhibit a so-called borderline QT interval was the number one reason for an erroneous overdiagnosis of LQTS in the Mayo Clinic series. On the other hand, a suspicious faint in the setting of even a borderline QT interval should compel an intense search for LQTS.

Thirdly, a multi-generational family history of every patient being evaluated for the possibility of LQTS must be obtained. For such pedigree construction a genetic counsellor, if available, would be helpful. Family history requires an itemization and explanation for the premature sudden death, unexplained accident, unexplained syncope secondary to Torsades des Points ventricular tachycardia is one of the strongest clinical determinants for not only a future faint but also a future ACA/SCD. As such, a meticulous interrogation of each and every spell is necessary to determine and decide whether it ‘sounded’ arrhythmic in origin. Importantly, patients with LQTS also have vaso-vagal-mediated (neurocardiogenic) syncope at the same rate as the general population. Vaso-vagal fainting should not be used to advance the patient’s pre-test probability. In fact, the combined phenotype of a vaso-vagal faint in a patient who then went on to exhibit a so-called borderline QT interval was the number one reason for an erroneous overdiagnosis of LQTS in the Mayo Clinic series. On the other hand, a suspicious faint in the setting of even a borderline QT interval should compel an intense search for LQTS.

Fourthly, although calls for pre-sports participation ECG screening and even universal ECG screening continue, it is paramount that the 12-lead ECG be scrutinized in the light of the answers obtained during the aforementioned steps. In addition, the normal sex- and age-dependent distribution in the heart rate-corrected QT interval (QTc) must be appreciated lest a so-called borderline QT prolongation be prematurely and erroneously translated as ‘possible LQTS’. As a reminder, a diagnostic pronouncement of LQTS should be rendered very seldom from inspection of an ECG alone. In fact, in the absence of any secondary causes, it is not until the QTc reaches 500 ms when the pre-test probability favours the identification of a host with LQTS over a host who is an extreme QTc outlier. Instead, it must be appreciated that the ECG may or may not always display evidence for abnormal cardiac repolarization as epitomized by prolongation in the index of cardiac repolarization, i.e. the QTc, which then generates a differential diagnosis that certainly includes LQTS among a large list of possibilities. Restraint should be exercised to avoid making the error of prematurely casting a diagnostic pronouncement of LQTS based on inspection of an ECG. Once the phrase, ‘LQTS or possible LQTS’ is uttered, the proverbial ‘jack’ is out of the box, and it is extremely difficult to reel that diagnosis back into the can.

As the QT rate correction goes, despite its acknowledged limitations especially at fast heart rates, the Bazett’s correction remains the one which provides the most useful clinical information as its abnormal values correlate well with augmented arrhythmic risk and with probability of being affected by LQTS. Regarding the length of repolarization, the computer-derived QTc must be confirmed manually as the computer’s QTc accuracy is about 80–90%, but underestimation becomes frequent when the return to baseline of the T-wave is slow. However, the performance of general cardiologists and even heart rhythm specialists, with respect to QTc interpretation, is often far from adequate. Assuming an accurate manual QTc has been made confirming or challenging the computer’s QTc, what QTc value is actionable? The answer continues to be disparate, and this is another root cause of LQTS overdiagnosis. Here is where the normal distribution in QTc values must be appreciated. While the probability of LQTS in the offspring of a mother with LQTS whose QTc is only 440 ms is 50%, that same QTc obtained as an incidental finding (screening ECG for example) in an asymptomatic adolescent with no family history has a <0.1% chance of indicating the presence of LQTS. In fact, even beyond the 99th percentile value for a woman, for example, a QTc of 481 ms in an asymptomatic woman with no family history, the positive predictive value for QTc is <10%. Thus, it is critical to bear in mind that such QTc values do not equal LQTS even if being awarded three points and a qualitative assignment of ‘intermediate probability’ in the cumulative diagnostic score known as the ‘Schwartz’ score. The potential for major QTc interpretative mishaps has intensified recently with the designation of QTc values ≥450 ms in men and ≥460 ms in women as ‘prolonged QTc’ values from the standpoint of AHA/ACC/HRS guidelines. These thresholds represent about 95th percentile values. Despite satisfying a guideline definition of ‘prolonged QTc’, unless advanced by additional data, the positive predictive value for QTc is <1%. In fact, the pre-test probability does not statistically favour LQTS over a QTc outlier in an otherwise asymptomatic host with no family history until the QTc approaches 500 ms.

Besides the length of repolarization, there is the look of repolarization that must be considered. Years ago one of us wrote ‘I don’t measure the QT interval, I look at it’. The second most common reason observed for overdiagnosis of LQTS was attributed to misces in sizing up the look of repolarization. Specifically, U-wave inclusion resulting in QT inflation was the primary mistake. On the other hand, there are subtle T-wave changes, particularly notched T waves in limb lead II or the precordial leads V4–V6 that should increase suspicion for LQTS (Figure 1). Although macroscopic T-wave changes like T-wave alternans would also compel a pursuit for LQTS, such ‘looks’ are seldom seen (Figure 1).
Table 1 1993–2012 long QT syndrome diagnostic criteria

<table>
<thead>
<tr>
<th>Electrocardiographic findings&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, QTc&lt;sup&gt;b&lt;/sup&gt; ≥ 480 ms</td>
<td>3</td>
</tr>
<tr>
<td>460–479 ms</td>
<td>2</td>
</tr>
<tr>
<td>450–459 (male) ms</td>
<td>1</td>
</tr>
<tr>
<td>B, QTc&lt;sup&gt;b&lt;/sup&gt; 4th minute of recovery from exercise stress test ≥ 480 ms</td>
<td>1</td>
</tr>
<tr>
<td>C, Torsade de pointes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
</tr>
<tr>
<td>D, T-wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>E, Notched T-wave in three leads</td>
<td>1</td>
</tr>
<tr>
<td>F, Low heart rate for age&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Clinical history

| A, Syncope<sup>e</sup>                  | 2      |
| With stress                             | 1      |
| Without stress                          | 0.5    |
| B, Congenital deafness                  |        |

Family history

| A, Family members with definite LQTS<sup>f</sup> | 1 |
| B, Unexplained sudden cardiac death below age 30 among immediate family members<sup>g</sup> | 0.5 |

SCORE: ≤1 point: low probability of LQTS. 1.5 to 3 points: intermediate probability of LQTS. ≥3.5 points high probability.

<sup>a</sup>In the absence of medications or disorders known to affect these electrocardiographic features.

<sup>b</sup>QTc calculated by Bazett’s formula where QTc = QT/√RR.

<sup>c</sup>Mutually exclusive.

<sup>d</sup>Resting heart rate below the 2nd percentile for age.

<sup>e</sup>The same family member cannot be counted in A and B (from ref.15).

As mentioned previously, the ‘Schwartz’ diagnostic score tabulates these aforementioned elements of the personal history, family history, and ECG QTc values to qualitatively frame an index of suspicion for LQTS and is helpful for the assessment of the index case and of family members. From the standpoint of actionability, a diagnostic score ≥3.5 makes the diagnosis very likely (P.J.S.) and should compel further investigation for the possibility of LQTS (M.J.A. and P.J.S.). However, just like the QTc issue, although this diagnostic score (≥3.5) makes the diagnosis much more likely, this cut-off value should not be confused as equalling the presence of LQTS (M.J.A.).

This score is dynamic. One of the most valuable and least expensive tests to perform with the objective to be able to revise the score and thereby refine the diagnosis, is serial ECG evaluations in the patient; also important is to obtain ECGs of the patient’s first-degree relatives. As one can imagine, the probability of LQTS in an index case can be augmented if one of those family members has a QTc of >460 ms and would increase dramatically if one of them is caught with a QTc of ≥480 ms. In the score, the presence of a family member already diagnosed as affected by LQTS adds 0.5 points which moves the total points to the threshold of 3.5 points in the case of a normal index case with three points provided by a QTc of ≥480 ms.

Fifthly, only following the aforementioned steps should the next tier of investigations be considered including 24-h ambulatory monitoring, treadmill/cycle stress testing, the epinephrine QT stress test (M.J.A.), abrupt standing (P.J.S.) and, finally, LQTS genetic testing. If not, each test may advance erroneously the case for LQTS. One of the biggest offenders is the misuse of ambulatory ECG monitoring. A night-time QTc of 500 ms in a subject with a baseline QTc <440 ms should not prompt an automatic diagnosis. The main value of Holter recordings lies in showing, especially at rest, specific morphologic alterations of the T-wave that are associated with LQTS.

Similar restraint needs to be exercised with the various stress tests as well. For the most part, provocative studies are best to confirm or unmask the presence of type 1 LQTS (LQT1). Specifically, abnormal QTc values in the recovery phase of stress testing (i.e. >470 ms at 2–3 min of recovery), paradoxical QT lengthening of the absolute QT interval during the Mayo Clinic epinephrine infusion protocol, or paradoxical lengthening of the QTc with the Shimizu epinephrine bolus protocol all increase the possibility of LQT1 with positive predictive values ≥70% and negative predictive values of 95%. However, as self-evident in their positive predictive value, a positive test response does not equal the diagnosis of LQTS in general, or LQT1 in particular. The tests may be complimentary and additive as we have numerous examples of LQT1-positive patients having a positive treadmill stress test but a negative epinephrine QT stress test and vice-versa (M.J.A.).

Lastly, this brings us to the rightful position of LQTS genetic testing in the diagnostic evaluation of LQTS, namely at the end of the investigation. Starting with LQTS genetic testing is reckless and dangerous reflecting a fundamental failure to recognize the probabilistic nature of genetic testing, the LQTS genetic test’s so-called background genetic noise rate and so forth. Currently, 13 LQTS-susceptibility genes explain nearly 80% of LQTS with mutations in the three canonical LQTS-susceptibility genes (KCNQ1, KCNH2, and SCN5A) that give rise to LQT1, LQT2, and LQT3 accounting for the vast majority of cases. Specifically, LQT1-3 account for ~75% of LQTS while LQT4-13 add an additional 5%. In the first HRS/EHRA guidelines for genetic testing of cardiomyopathies and channelopathies, LQTS genetic testing was recommended for: (i) patients in whom the cardiologists had achieved an index of clinical suspicion for LQTS based on their impression following the first four steps outlined previously, and this is largely equivalent to a score ≥3.5 points; (ii) asymptomatic patients with no family history who nevertheless have serial ECGs evidencing a QTc in the 500 ms range; and (iii) appropriate relatives when a definite LQTS-causative mutation has been established in the proband. Finally, LQTS genetic testing may be considered for the asymptomatic host with no family history but serial ECGs with a QTc in the range of 470 ms or greater. Of course, as the stringency of QTc/LQTS phenotype is decreased, the possibility for a false-positive genetic test increases.

Here is where a correct understanding of the yield of genetic testing and the background noise rate can sharpen a cardiologist’s diagnostic precision. An LQTS expert who has made a definite clinical diagnosis of LQTS will not be swayed by a negative genotype, which occurs in 25% of ‘unquestionable LQTS’. On the other hand, a general cardiologist who often orders LQTS genetic testing and is still waiting for his/her first positive genetic test should reassess probably his/her diagnostic skills and begin
to wonder whether the phenotypic constitution of the patient being used to draw a conclusion of LQTS is flawed. Finally, there may be times where LQTS genetic testing can be utilized in an attempt to mount evidence to move away from the diagnosis of LQTS. Although the genetic test cannot exclude the diagnosis of LQTS all by itself, it is an independent, objective measure that does ‘rule out’ 75–80% of LQTS and in so doing, a negative genetic test can be concordant with a second/third opinion assessment for lack of evidence in situations where the diagnosis might have been cast prematurely by the first cardiologist.6

The identification of a patient’s probable LQT1-, LQT2-, or LQT3-causative mutation has clear diagnostic, prognostic, and therapeutic implications.3–5 Further, intragenic risk stratification and even mutation-specific risk stratification26–28 are being incorporated which further refines the ability to design an individualized/personalized treatment programme for patients with LQTS. The next section details the various treatment strategies ranging from no-therapy to drug therapy to denervation therapy to device therapy and the composite of clinical, electrocardiographic, genetic, and molecular/cellular determinants that go into devising the right therapy for the right patient delivered at the right time.

**Clinical management and treatment strategies**

The success of therapy is a reflection of the understanding of any given disease. In the case of LQTS, the key elements of management are β-adrenergic blocking agents, left cardiac sympathetic denervation (LCSD), the implantable cardioverter-defibrillator (ICD), and common sense. They are complemented currently by gene-specific approaches, both pharmacological and behavioural, and hopefully in a not too distant future also by mutation-specific approaches.
**β-Adrenergic blockade**

β-Adrenergic blocking agents have represented the first-choice therapy for symptomatic LQTS patients since the mid-1970s,\(^1\) barring specific contraindications. Excessive bradycardia is very seldom a concern, especially if the dosage is uptitrated gradually over several weeks. Not all β-blockers are equally effective and the two producing the least LQTS-associated recurrences are propranolol and nadolol.\(^29\) Propranolol remains the most widely used especially for infants and children, at 2–4 mg/kg/day divided two to three times per day depending on its formulation; this dosage may be increased if necessary. Nadolol is also used very often as its longer half-life allows once-a-day administration in adolescents and adults, which is very important for compliance usually at 0.75–1.5 mg/kg/day. However, twice-a-day nadolol administration is favoured to obtain a more uniform plasma concentration. Metoprolol has been associated with a higher risk of recurrences\(^29\) and cannot be recommended for symptomatic patients. Atenolol seems somewhat less effective but the data available are limited.\(^30\) Differences in blockage of late/sustained Na\(^+\) current may play a role in the different clinical efficacy of various β-blockers, and this effect is highest for propranolol, lower but present for nadolol, and completely absent for metoprolol.\(^31\) Unfortunately, due to limited commercial interest, nadolol is no longer available, or is available with difficulty, in many countries. A joint action by Cardiological Societies and by individual cardiologists with the various Ministries of Health could help in making available this life-saving drug that cannot be easily substituted.

In 869 LQTS 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) and without events in the first year of life.\(^32\) There is clear evidence that β-blockers are extremely effective in LQT1 patients. Data from two large studies\(^33,34\) indicate that mortality is around 0.5% and sudden death combined with cardiac arrest reaches 1%. β-Blocker non-compliance and use of QT-prolonging drugs are responsible for almost all life-threatening ‘β-blocker failures’ in LQT1 patients.\(^34\) Conversely, compliance with β-blocker therapy and avoidance of QT-prolonging drugs is associated with 97% reduction in the risk for cardiac events.

Compared with LQT1, LQT2 patients have more life-threatening events despite β-blockers, but most of these are resuscitated cardiac arrests (6–7%) rather than a tragic β-blocker breakthrough of sudden death.\(^33\) Among LQT3 patients, major events have been reported to occur more frequently (10–15%) despite β-blockers\(^34,35\) and have contributed to the incorrect notion that β-blockers are of limited or no value for LQT3 patients and could potentially be pro-arrhythmic. As already discussed,\(^36\) this misconception is due to the fact that, given the small numbers of LQT3 patients in any study, investigators have pooled together the data independently of the age at which the first cardiac event has occurred. Indeed, cardiac events in the first year of life are associated with an extremely poor prognosis independent of treatment whereas for the remaining LQT3 patients, their mortality on β-blocker therapy appears to be close to 3% and seems to be largely related to those with QTc values ≥ 600 ms. This information comes from the largest study ever performed in LQT3, with data on 400 patients (Wilde et al., unpublished data, 2013). Most LQT3 patients, except the very high-risk symptomatic LQT3 infants, respond well to LCSD.\(^36–38\) Patients with the severe Jervell and Lange-Nielsen or Timothy syndrome often are not adequately protected by β-blockers and require additional protection.\(^3,39\)

**Left cardiac sympathetic denervation**

Left cardiac sympathetic denervation, performed either by an extrapleural approach which makes thoracotomy unnecessary\(^40\) or by thoracoscopy,\(^38\) requires removal of the first 4 thoracic ganglia (T1–T4). The cephalic portion of the left stellate ganglion should be left intact to avoid Horner’s syndrome. Whenever the local surgeons do not have adequate personal experience with either the extrapleural or with videoscopic LCSD, the traditional and easy approach represented by opening the second left intercostal space allows a clear visualization of the stellate ganglion with the sympathetic chain (P.J.S.). The Mayo Clinic experience, with over 110 videoscopic LCSDs to date in LQTS patients ranging in age from 4 weeks to 82 years, indicates that there is no age limitation for the videoscopic approach. M.J.A. always favours the latter approach. The rationale for LCSD, largely based on its rather striking antiarrhythmic effect,\(^41\) has been reviewed recently,\(^42\) and includes a major reduction in norepinephrine release at ventricular level with the absence of post-denervation supersensitivity,\(^43\) and no reduction in heart rate.\(^44\)

The largest series on LCSD was published in 2004 and included 147 LQTS patients who underwent sympathectomy during the last 35 years.\(^37\) They represented a group at very high risk [99% symptomatic, with an extremely long mean QTc (563 ± 65 ms), previous cardiac arrest in 48%, and recurrent syncope despite full-dose β-blockers in 75%]. During a mean follow-up of 8 years, there was a 91% reduction in cardiac events. In five patients who underwent LCSD due to multiple ICD shocks and electrical storms, over a 4-year follow-up, there was a 95% decrease in the number of shocks with a dramatic improvement in the quality of life of the patients and of their families. LCSD produced a mean QTc shortening of 39 ms, pointing to an action on the substrate as well as on the trigger (i.e. localized norepinephrine attenuation). The unavoidable conclusion is that whenever syncopal episodes recur despite a full-dose β-blocker therapy, LCSD should be considered and implemented without hesitation. Failure by the attending physician to provide the family with adequate information of the pros and cons of LCSD vs. ICD implant may also carry medico-legal consequences.\(^45\) Our current indications for denervation therapy include: (i) patients with appropriate VF-terminating ICD shocks, (ii) patients with LQTS-triggered breakthrough cardiac events while on adequate drug therapy, (iii) patients with failure to tolerate β-blocker therapy because of unacceptable side-effects or because of asthma, and (iv) high-risk young patients where primary drug therapy may not be sufficiently protective, with hopes to serve as a ‘bridge to an ICD’.\(^38\)

**Implantable cardioverter defibrillator**

When dealing with high-risk patients, clinical cardiologists are often ‘trigger happy’ when it comes to recommending an ICD implant. In the case of appropriate shocks, he/she will have saved the life
of the patient; in case of no shocks and possibly of complications, he/she will have ‘done the best’ for the patient’s protection. No one could argue against such positive goals. Conversely, without the support of a very strong rationale, the decision of not implanting an ICD could carry medico-legal consequences in the case of a tragic outcome. Even though these considerations should not affect medical decisions, in the era of ‘defensive medicine’, they actually do. The current situation should be analysed in the light of this reality. Currently, there is a stunning mismatch in ICD utilization for patients with LQTS, with some programmes in the USA implanting an ICD in ~80% of their patients with LQTS, while among two of the largest LQTS Clinics in the world our ICD utilization rate is ~3% (P.J.S.) and 15% (M.J.A.).

There is an overall consensus for immediately implanting an ICD in the case of a documented cardiac arrest, either on or off therapy, even though some exceptions exist such as in a clear case of a drug-induced event in an otherwise asymptomatic patient with modest QT prolongation. In contrast, opinions differ strongly regarding the use of ICDs in patients without cardiac arrest.

The current knowledge is essentially based on the largest ICD study published so far, which provided information on 233 LQTS patients. It is disquieting to realize that the majority of implanted patients had not suffered a cardiac arrest and, moreover, that many had not even failed β-blocker therapy. Asymptomatic patients, almost absent among the LQT1 and LQT2 groups, represented 45% among LQT3 patients, indicating that the mere presence of an SCN5A mutation, even in an asymptomatic individual, was deemed sufficient for ICD implant. During a mean follow-up of 4.6 years, at least one appropriate shock was received by 28% of patients and adverse events occurred in 25% of them. Given the practical importance to identify in advance those patients with the highest and lowest probability to receive appropriate shocks, which represents the justification for the ICD implant, a score (M-FACT) was developed based on simple clinical variables available in a doctor’s office during a first visit (Table 2). M-FACT considers QTc duration, age at implant, cardiac events despite therapy. Appropriate ICD therapies were predicted by age <20 years at implantation, a QTc >500 ms, prior cardiac arrest and cardiac events while on drug therapy; within 7 years, appropriate shocks occurred in no patients with none of these factors and in 70% of those with all factors. Similar observations have been drawn from the largest single-centre study of ICD use in patients with LQTS.

We suggest to implant an ICD in (i) all patients who survived a cardiac arrest while compliant on adequate drug therapy; (ii) most of those who survived a cardiac arrest except those with a reversible/preventable cause, and possibly some of those with previously undiagnosed and therefore untreated LQT1; (iii) those with LQTS-triggered syncpe despite a full dose of β-blocker, whenever the option of LCSD is either not available or discarded after discussion with the patients; (iv) all patients with syncope, despite a full dose of β-blocker and LCSD; (v) exceptionally, asymptomatic postpubertal women with LQT2 and a QTc ≥550 ms and asymptomatic patients with a QTc >550 ms who also manifest signs of high electrical instability (e.g. T-wave alternans) or other evidence of being at high risk despite β-blockade and LCSD (e.g. long sinus pauses followed by abnormal T-wave morphologies). For patients with Jervell and Lange-Nielsen or Timothy syndrome, who appear incompletely protected by anti-adrenergic therapies, we recommend to consider, in a case-by-case approach, the possibility of triple therapy, namely β-blockers plus LCSD plus ICD.

**Gene-specific therapy and management**

The progressive unravelling of the genotype–phenotype correlation has allowed LQTS to become the first disease for which initial steps for gene-specific management have become possible and is opening previously unforeseen preventive and therapeutic strategies. LQT1 patients are at higher risk during sympathetic activation, such as during exercise and emotions. They should not participate in competitive sports (P.J.S.). Probably, they should also avoid intense exercise training to avoid the potentiation of potentially dangerous vagal reflexes (P.J.S.). In contrast, according to M.J.A., these limitations may not be necessary for an athlete who has been diagnosed, risk stratified, treated, and counselled carefully and extensively. Swimming, well known since long time to often trigger cardiac events in LQTS, is particularly dangerous for LQT1 patients, as 99% of the arrhythmic episodes associated with swimming occur in this group. LQT2 patients are very sensitive to serum potassium levels, which should not be allowed to fall. When reasonable levels are not maintained by diet or by oral K+ supplements, a combination with K+ sparing agents such as spironolactone should be considered. As these patients are at higher risk especially when aroused from sleep or rest by a sudden noise, we recommend that telephones and alarm clocks are removed from their bedrooms. Also when parents in the morning have to wake up their children, they should do it gently and without yelling. This combines good manners and gene-specific management. Women with LQT2, but not with LQT1, are at increased risk during the postpartum period and compliance with LQT2-directed therapy, adequate rest, and avoidance of QT prolonging medications is important particularly during this time. If a mother chooses not to breastfeed, we recommend that the male partners of LQT2 mothers take care of night-time feeding during the first

<table>
<thead>
<tr>
<th>Table 2</th>
<th>M-FACT risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event free on therapy for &gt;10 years</td>
<td>Yes</td>
</tr>
<tr>
<td>QTc (ms)</td>
<td>≤500</td>
</tr>
<tr>
<td>Prior ACA</td>
<td>No</td>
</tr>
<tr>
<td>Events on therapy</td>
<td>No</td>
</tr>
<tr>
<td>Age at implant</td>
<td>&gt;20 years</td>
</tr>
</tbody>
</table>

*Acronym derived from M (Minus 1 point for being free of cardiac events while on therapy for >10 years); F (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 ref.46).*
Asymptomatic long QT syndrome patients and patients with a normal QTc

As the first manifestation of QTc in ~13% of cases is sudden death, β-blocker treatment ideally should be initiated in all LQTS patients with manifest QT prolongation including those still asymptomatic. Possible exceptions could be asymptomatic LQT1 men who were diagnosed after 40 years because they seldom have a first event after this age and possibly any symptomatic LQTS host who is older than 50 years and has a resting QTc > 500 ms. However, LQT2 women remain at risk throughout life, and it is prudent to always treat them, with few exceptions.

Genetically proven LQTS patients with so-called normal QT interval LQTS or concealed LQTS (i.e. QTc < 440 ms) constitute >25% of the LQTS population and have a markedly lower risk for life-threatening events compared with phenotypically affected patients but are at comparatively higher relative risk, albeit still very low absolute risk, than their genotype negative, unaffected family members. While we still recommend the simple preventive measures of QT drug avoidance, electrolyte/hydration replenishment particularly in the setting of vomiting and diarrheal illnesses where hypokalemia could occur, and use of antipyretics to lower fever, active therapy with prophylactic β-blockers may not be necessary but this is decided on a case by case approach. For example, among LQT1 and LQT3 patients with a normal QT interval, since those with missense mutations in the transmembrane regions have a non-negligible risk of life-threatening arrhythmias, prophylactic drug therapy may be recommended. In addition, an asymptomatic LQT1 patient, with normal QT intervals at rest but evidencing maladaptive QTc parameters during the stress test’s recovery phase or clear paradoxical QT prolongation during epinephrine infusion (M.J.A.), cannot be classified as having non-penetrant (and therefore zero risk) LQT1. Accordingly, an attempt at prophylactic β-blocker therapy would be considered and if acceptably tolerated, continued. Increasingly, a mutation-specific evaluation should integrate the clinical evaluation whenever possible.

Annual follow-up visits of all symptomatic and asymptomatic patients with LQTS, and of their children, are strongly recommended to monitor the stability of their condition. We have often seen even dramatic signs of increased electrical instability or other pointers to high risk in still asymptomatic patients not present 1-year earlier; these findings have led to important readjustments in therapy resulting in the maintenance of an unethical life. For the asymptomatic adult with QT5 and no changes in their health, we have begun to see these patients every other year after the age of 22 years (M.J.A.) which has resulted in significant cost savings without compromising their care.

Conclusions

We have expressed our personal views about how to approach diagnosis and treatment in patients affected, or possibly affected, by LQTS. In the very limited areas where our opinions differ, instead of blunting them through compromise, we have chosen to clearly identify our respective positions, which we mutually respect.

Most of the time what is necessary for a correct management of these patients is rather straightforward, and what had been described above will be sufficient, but there are times when the decisions are truly complex and generate deep concerns because we are fully aware of the implications of our potential errors. Typical difficulties relate to infants with very severe presentations and with asymptomatic or mildly symptomatic children for whom, for a variety of reasons, we suspect that pharmacological treatment may not be sufficient and, on the other hand, we are concerned with the drawbacks of early ICD implants. To our colleagues who may see LQTS patients only occasionally we say that, when in doubt, the most appropriate path is to consult with experts in

3–4 months postpartum. Importantly, no woman with LQTS should be told that they should not have children because of their LQTS. We have encountered too many women who have received such cruel and unacceptable counselling.

The demonstration that LQT3-causing SCN5A mutations have a ‘gain-of-function’ effect suggested to test sodium-channel blockers, particularly mexiletine, as possible adjuvants in the management of LQT3 patients. The effect of mexiletine is mutation specific and that is why the efficacy of mexiletine should be tested in all LQT3 patients under continuous ECG monitoring by the acute oral drug test technique, using half of the daily dose. Within 90 min the peak plasma concentration is reached and if the QTc is shortened by more than 40 ms, without evidence of PR prolongation, QRS widening, and eliciting a Brugada ECG pattern, then mexiletine could/should be added to β-blocker therapy. Flecainide has been considered but, because of its blocking effects and of its potential of unmasking the Brugada syndrome, cannot be advised for the treatment of LQTS patients. Even though there is no conclusive evidence for a beneficial effect of mexiletine and definite failures have occurred, there is also growing evidence of significant benefit in a number of individual cases. Highly malignant forms manifesting in infancy due to mutations causing extremely severe electrophysiological dysfunctions which were corrected by the combination of mexiletine and propranolol have been reported. Despite very limited information, there are hopes for the potential benefit of ranolazine, a sodium-channel blocker especially specific for the late sodium current. With respect to β-blocker therapy, given its direct late sodium current blocking properties, propranolol is probably the LQT3-preferred β-blocker.

Independently of genotype, all LQTS patients should avoid any cardiac or non-cardiac drug that blocks the icurrent. A list of such drugs is available at www.qtdrugs.org and should be given to every patient because their family physician/local medical provider may not be aware of this potentially lethal, unwanted side effect. This is a precise responsibility of the cardiologist who follows these patients. However, there may be times when a patient with LQTS needs to be treated with such a medication. An example is that of an LQTS patient with concomitant schizophrenia who needs antipsychotic therapy. In such situations, the risks and benefits should be analysed and reviewed carefully and the joint decision to use a drug with known QT prolonging potential should be documented.
the field: it is never wrong in medicine to admit ‘limited knowledge or experience’ in a specific case, if this is followed by the appropriate next steps. Here, we wish to share with them that we, despite many years spent dealing with LQTS and our daily encounters with these families, not infrequently send out emails to each other and three to four of our most respected colleagues throughout the world and, often within hours, receive extremely important advice that either supports or modifies our plans for these patients. If we do it, everyone else can.

Acknowledgements

The authors are grateful to Pinuccia De Tomasi, BS, for expert editorial support.

Funding

M.J.A. is a consultant for Boston Scientific, Medtronic, St. Jude Medical, and Transgenic. Intellectual property derived from MJA’s research program resulted in license agreements in 2004 between Mayo Clinic Health Solutions (formerly Mayo Medical Ventures) and PGxHealth (formerly Genomics Pharmaceuticals and now Transgenic). However, none of these companies including Transgenic contributed directly to this work in any manner. P.J.S. has no conflict of interest to disclose.

References

30. Chatrath R, Bell CM, Porter CJ, Ackerman MJ. β-Blocker therapy failures in pro-

not explain its efficacy in the long QT syndrome. J Cardiovasc Pharmacol

Locati EH, Priori SG, Napolitano C, Medina A, Zhang L, Robinson JL, Timothy K,
Towbin JA, Andrews ML. Effectiveness and limitations of beta-blocker therapy

33. Priori SG, Napolitano C, Schwartz PJ, Grillo M, Bloise R, Rannetti E, Moncalvo C,
Tulipani C, Vea A, Bottelli G, Nastoli J. Association of long QT syndrome loci
and cardiac events among patients treated with beta-blockers. JAMA 2004;292:
1341–1344.

34. Vincent GM, Schwartz PJ, Denjoy I, Swan H, Beitel C, Spazzolini C, Crotti L,
Pippo K, Lupoglazoff JM, Villain E, Priori SG, Napolitano C, Zhang L. High efficacy
of beta-blockers in long-QT syndrome type 1: contribution of noncompliance

Denjoy I, Guicheny P, Breithardt G, Keating MT, Towbin JA, Beggs AH,
Brink P, Wilde AA, Toivonen L, Zareba W, Robinson RJL, Timothy KW,
Corfield V, Wattanasirichaigoon D, Corbett C, Haverkamp W, Schulze-Bahr E,
Lehmann MH, Schwartz K, Counel P, Bloise R. Genotype-phenotype correlation

36. Schwartz PJ, Spazzolini C, Crotti L. All LQT3 patients need an ICD. True or false?
Heart Rhythm 2009;6:113–120.

37. Schwartz PJ, Priori SG, Cerrone M, Spazzolini C, Odore A, Napolitano C,
Bloise R, De Ferrari GM, Klery C, Moss AJ, Zareba W, Robinson RJL, Hall WJ,
Brink PA, Toivonen L, Epstein AE, Li C, Hu D. Left cardiac sympathetic denerv-
ation in the management of high-risk patients affected by the long QT syndrome.

38. Collura CA, Johnson JN, Moir C, Ackerman MJ. Left cardiac sympathetic denerv-
ation for the treatment of long QT syndrome and catecholaminergic polymorphic
ventricular tachycardia using video-assisted thoracic surgery. Heart Rhythm 2009;
6:752–759.

Berul CI, Binner-Gracilic M, Toivonen L, Horige M, Schulze-Bahr E, Denjoy I. The
Jervell and Lange-Nielsen syndrome. Natural history, molecular basis, and clinical

40. Odoro A, Bozanni A, De Ferrari GM, Schwartz PJ. Left cardiac sympathetic
denervation for the prevention of life-threatening arrhythmias: the surgical supracla-
vicular approach to cervicothoracic sympathectomy. Heart Rhythm 2010;7:
1161–1165.

41. Schwartz PJ, Snebold NG, Brown AM. Effects of unilateral cardiac sympathetic
denervation on the ventricular fibrillation threshold. Am J Cardiol 1976;37:
1034–1040.


43. Schwartz PJ, Stone HL. Left stellatotomy and denervation supersensitivity in con-

44. Schwartz PJ, Stone HL. Effects of unilateral stellatotomy upon cardiac performance

45. Schwartz PJ. Efficacy of left cardiac sympathetic denervation has an unforeseen

46. Schwartz PJ, Spazzolini C, Priori SG, Crotti L, Vicentini A, Landolina M,
Gasparini M, Wilde AAM, Knops RE, Denjoy I, Toivonen L, Manning G,
Al-Fayadhi M, Jordans L, Borggreve M, Holmgren C, Brugada P, De Roy L,
Hohnloser SH, Brink P. Who are the long-QT syndrome patients who receive
an implantable cardioverter defibrillator and what happens to them? Data from the European long-QT syndrome implantable cardioverter-

47. Homay JM, Knoshta M, Webster TL, Haglund CM, Friedman PA, Ackerman MJ.

Zipes DP, Jalife J (eds), Cardiac Electrophysiology. From Cell to Bedside, 4th ed. Phila-

49. Crotti L, Spazzolini C, Porretta AP, Dagradi F, Taravelli E, Pettacci B, Vicentini A,

50. Johnson JN, Ackerman MJ. Competitive sports participation in athletes with con-


52. Choi G, Kopplin LJ, Tester DJ, Will ML, Haglund CM, Ackerman MJ. Spectrum
and frequency of cardiac channel defects implicated in swimming-triggered arrhythmia

53. Khoshtaei A, Tester DJ, Will ML, Bell CM, Ackerman MJ. Identification of a
common genetic substrate underlying postpartum cardiac events in congenital

54. Heraden MJ, Goosen A, Toivonen L, Zareba W, Robinson JL, Timothy KW,
Denjoy I, Guicheney P, Breithardt G, Keating MT, Towbin JA, Beggs AH.
Does pregnancy increase cardiac risk for LQT1 patients? J Am Coll Cardiol

55. Bennett PB, Yazzawa K, Makita N, George AL Jr. Molecular mechanism for an

56. Schwartz PJ, Priori SG, Locati EH, Napolitano C, Cantu F, Towbin JA, Keating MT,
Hammoude H, Brown AM, Chen LS. Long QT syndrome patients with mutations of
the SCN5A and HERG genes have differential responses to Na+ channel

57. Ruan Y, Liu N, Bloise R, Napolitano C, Priori SG. Gating properties of SCN5A
mutations and the response to mexiletine in long-QT syndrome type 3 patients.


of flecainide in patients with new SCN5A mutation: mutation-specific therapy for

60. Wang DW, Kiyouse T, Sato T, Arita M. Comparison of the effects of class I anti-
arrhythmic drugs, cibenzoline, mexiletine and flecainide, on the delayed rectifier
K+ current of guinea-pig ventricular myocytes. J Mol Cell Cardiol 1996;28:
893–903.

61. Wang DW, Crotti L, Shimizu W, Pedrazzini M, Cantu F, De Filippo P, Kishiki K,
Miyazaki A, Ikeda T, Schwartz PJ, George AL Jr. Malignant perinatal variant of