Addressing the diagnostic and therapeutic challenges in inheritable arrhythmia syndromes: with emphasis on the pediatric population

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Chapter 4

Diagnosis of Congenital Long QT Syndrome: Do All Clinically Suspected Patients Warrant Genetic Testing?

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Abstract

Introduction: Diagnosis of congenital long QT syndrome (LQTS) involves clinical, electrocardiographic (ECG) and genetic evaluation. Genetic testing however has the disadvantages of not being uniformly available and being costly and time-consuming. We aimed to investigate if all patients clinically suspected with LQTS warrant genetic testing.

Methods: Unrelated probands referred for genetic counselling and predictive testing for LQTS (KCNQ1/KCNH2/SCN5A/KCNE1/KCNE2/KCNJ2) were included. Schwartz score (SS) was derived for all patients. Maximum QTc on the earliest available Holter recording (QTcH) was obtained for patients with SS ≤3. QTc/QTcH >450 ms was considered prolonged.

Results: Study cohort (n=214, 68% females, 78% symptomatic, age 31±21 years, heart rate 73±19 bpm, QTc 478±64 ms) consisted of 93 mutation carriers (35% LQT1, 47% LQT2, 16% LQT3 and 2% LQT7). Of patients with SS >3 (n=103), 77 (75%) were mutation carriers. Among patients with SS ≤3 and prolonged QTc (n=32), 9 (28%) were mutation carriers. Among patients with SS ≤3 and normal QTc (n=79), QTcH was normal in 16, all of whom did not carry a putative pathogenic mutation; QTcH was prolonged in 63 patients, 7 (11%) of whom were mutation carriers. Among patients with SS ≤3 and resting QTc ≤450 ms, QTcH cut-off of 450 ms was 100% sensitive in predicting genotype-positivity, although the specificity was low.

Conclusions: In patients presenting with a questionable LQTS phenotype and a nondiagnostic resting QTc, normal Holter QTc is highly effective in ruling-out LQTS, especially when genetic testing is not readily available or feasible.
Introduction

Congenital long QT syndrome (LQTS) encompasses a group of hereditary cardiac channelopathies associated with syncope, sudden cardiac death (SCD) and abnormal cardiac repolarization manifesting as prolonged QT interval on the electrocardiogram (ECG). Clinical diagnostic criteria are often used to assess the likelihood of LQTS in a patient. While the typical LQTS patients provide no diagnostic difficulty, it is the borderline cases that are more complex and require the evaluation of multiple variables besides clinical presentation and ECG. Although genetic testing has become available as a diagnostic tool in the last decade, the costs involved and the lack of uniform availability continue to be the drawbacks of the test. The purpose of this study was to investigate if all clinically suspected LQTS patients warrant genetic testing.

Methods

Study population

The study population included 214 unrelated probands referred for genetic counselling and predictive testing for LQTS genes (KCNQ1/KCNH2/SCN5A/KCNE1/KCNE2/KCNJ2). Family members of probands were not included in the study.

Data collection

Demographic and clinical characteristics including age, gender, pertinent cardiac symptoms and relevant family history were recorded. From the earliest available standard 12-lead ECG prior to initiation of therapy, the heart rate (HR) was recorded. The QT interval was measured manually from the beginning of the QRS complex to the end of the T wave in lead II or V5. The end of the T wave was determined as the intersection point between the isoelectric baseline and the tangent representing the maximal downward slope of the positive T wave or maximal upward slope of the negative T wave. The mean of three consecutive QT intervals was used. Corrected QT interval (QTc) was obtained using the Bazett’s formula. Subjects were grouped based on the revised Schwartz score (SS) as high SS (3.5 points, high probability of LQTS), intermediate SS (1.5–3 points, intermediate probability of LQTS) and low SS (1 point, low probability of LQTS). Since patients with High SS had a robust phenotype and a high probability of LQTS, their Holter analysis was not expected to add significant information; we proceeded with Holter analysis of the remaining patients. From the earliest available Holter recording, the longest QTc in the 24-hour period (QTcH) was recorded. QTc and QTcH >450 ms were considered prolonged. As this study was intended to focus only on the QTc in the ECG and the QTcH in the Holter recording, analyses of other variables such as T wave morphology and subclinical rhythm abnormalities were beyond the scope of the study and were not performed. Genetic screening had been performed in our laboratory as outlined previously. The results of genetic testing were documented, considering only those patients with known pathogenic mutations as mutation carriers; patients with mutations of unknown
pathogenicity and those with negative genotyping results were grouped as genotype-
negative patients.

Statistical Analysis
Continuous variables are presented as mean ± standard deviation (SD) and categorical
variables as number of patients (n) and percentage (%). Student’s t test was used to
compare continuous data and the χ² test for categorical data. Comparison of more than 2
groups of subjects was performed using ANOVA. All statistical analyses were performed
using SPSS 18.0 (SPSS Inc., Chicago, IL); p ≤0.05 was considered statistically significant.

Results
The age of the study cohort (n=214) at the time of genetic testing was 31±21 years
(range 0-85 years) and 146 (68%) were female. The reasons for referral were LQTS-
related symptoms in 167 (78%) patients, family history of SCD in 35 (16%) patients
and incidental observation of prolonged QTc in 12 (6%) patients (Figure 1). The HR
of the cohort was 73±19 bpm and the QTc 478±64 ms. Table 1 gives a comparison of
the 3 groups of subjects based on SS. Genetic testing revealed 93 (43%) patients to be
mutation carriers of whom 35% had LQT1, 47% had LQT2, 16% had LQT3 and 2% had
LQT7. The sensitivity and specificity of High SS in identifying mutation carriers in the
total cohort was 83% and 79% respectively.

Patients with SS ≤3 (n=111) were grouped based on their QTc as prolonged
QTc (n=32, 29%) and normal QTc (n=79, 71%). SS, HR, QTc and QTcH differed
significantly between the two groups (Table 2). Genetic testing revealed 9 (28%)
patients with a prolonged QTc and 7 (9%) patients with a normal QTc to be mutation
carriers (p=0.009). SS (2.2±0.99 vs. 1.4±0.97, p=0.005), QTc (455±29 vs. 431±33,
p=0.006) and QTcH (533±57 vs. 490±49, p=0.002) differed significantly between the
mutation carriers (n=16) and the genotype-negative patients (n=95). The sensitivity
and specificity of prolonged QTc in identifying mutation carriers was 56% and 76%
respectively in this group of patients with SS ≤3.

Figure 1. Reasons for referral for genetic testing
Among patients with SS ≤3 and normal QTc (n=79), there was a trend for lower heart rate (59±11 vs. 71±16), longer QTc (428±17 vs. 416±19) and longer QTcH (518±48 vs. 482±45) among the mutation carriers (n=7) compared to the genotype-negative patients (n=72). Of the patients in this group with a normal QTcH (n=17, QTcH 424±14 ms), none carried a putative pathogenic mutation; of those with a prolonged QTcH (n=62, QTcH 502±37 ms), 7 (11%) were mutation carriers (presented with: VF in 1, TdP in 1, palpitations in 1, syncope in 2, and family history of SCD in 2). QTcH cut-off 450 ms had a sensitivity of 100% and a specificity of 22% in identifying mutation carriers in this group of patients with normal QTc (Table 3).

Table 1. Clinical characteristics of the study cohort

<table>
<thead>
<tr>
<th></th>
<th>High SS</th>
<th>Intermediate SS</th>
<th>Low SS</th>
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<tr>
<td></td>
<td>n=103</td>
<td>n=57</td>
<td>n=54</td>
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<tr>
<td>Females, n (%)</td>
<td>72 (70)</td>
<td>43 (75)</td>
<td>31 (57)</td>
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<tr>
<td>Age at genetic testing, years</td>
<td>36 ± 22</td>
<td>27 ± 21</td>
<td>27 ± 17</td>
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<tr>
<td>Syncope, n (%)</td>
<td>36 (35)</td>
<td>23 (40)</td>
<td>18 (33)</td>
</tr>
<tr>
<td>VT/VF/ACA, n (%)</td>
<td>33 (32)</td>
<td>10 (18)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Family history SCD, n (%)</td>
<td>20 (19)</td>
<td>14 (25)</td>
<td>16 (30)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>70 ± 20</td>
<td>78 ± 20</td>
<td>71 ± 17</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>525 ± 55</td>
<td>448 ± 36</td>
<td>420 ± 22</td>
</tr>
<tr>
<td>Mutation carriers, n (%)</td>
<td>77 (75)</td>
<td>12 (21)</td>
<td>4 (7)</td>
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</table>

ACA, aborted cardiac arrest; ns, not significant; SCD, sudden cardiac death; SS, Schwartz score; VF, ventricular fibrillation; VT, ventricular tachycardia

Table 2. Clinical characteristics of patients with Schwartz score ≤3

<table>
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<tr>
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<th>QTc&gt;450 ms</th>
<th>QTc≤450 ms</th>
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<tr>
<td></td>
<td>n=32</td>
<td>n=79</td>
</tr>
<tr>
<td>Females, %</td>
<td>23 (72)</td>
<td>51 (65)</td>
</tr>
<tr>
<td>Syncope, n (%)</td>
<td>9 (28)</td>
<td>33 (42)</td>
</tr>
<tr>
<td>VT/VF/ACA, n (%)</td>
<td>2 (6)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Schwartz score</td>
<td>2.55 ± 0.74</td>
<td>1.09 ± 0.77</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>85 ± 21</td>
<td>70 ± 16</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>477 ± 20</td>
<td>417 ± 19</td>
</tr>
<tr>
<td>QTcH, ms</td>
<td>523 ± 57</td>
<td>485 ± 47</td>
</tr>
<tr>
<td>Mutation carriers, n (%)</td>
<td>9 (28)</td>
<td>7 (9)</td>
</tr>
</tbody>
</table>

ACA, aborted cardiac arrest; ns, not significant; QTcH, maximum QTc on Holter; SS, Schwartz score; VF, ventricular fibrillation; VT, ventricular tachycardia

Among patients with SS ≤3 and normal QTc (n=79), there was a trend for lower heart rate (59±11 vs. 71±16), longer QTc (428±17 vs. 416±19) and longer QTcH (518±48 vs. 482±45) among the mutation carriers (n=7) compared to the genotype-negative patients (n=72). Of the patients in this group with a normal QTcH (n=17, QTcH 424±14 ms), none carried a putative pathogenic mutation; of those with a prolonged QTcH (n=62, QTcH 502±37 ms), 7 (11%) were mutation carriers (presented with: VF in 1, TdP in 1, palpitations in 1, syncope in 2, and family history of SCD in 2). QTcH cut-off 450 ms had a sensitivity of 100% and a specificity of 22% in identifying mutation carriers in this group of patients with normal QTc (Table 3).
The distribution of QTcH based on mutation carriership in patients with QTc ≤450 ms is shown in Figure 2. Of note, all patients incidentally detected with prolonged resting QTc (n=12, SS 1.4±1.1, HR 85±26 bpm, QTc 453±29 ms) had Holter examinations (QTcH 488±44 ms), and only one (8%) of the patients was genotype-positive.

**Discussion**

Due to its profound phenotypic heterogeneity, the precise diagnosis of LQTS has remained a challenge, particularly in patients who do not exhibit the characteristic clinical and electrocardiographic features. Understandably, the diagnostic dilemma is many fold in probands than in family members of genotyped patients. Even with the usefulness and clinical applicability of genetic testing rapidly increasing, it is still restricted by its cost, availability and complexity involved in the interpretation of the results. Our study specifically addresses the issue of whether all suspected LQTS probands, especially the cases with incomplete QTc penetrance, should be subjected to genetic testing.

Given the poor sensitivity of the clinical scoring system in patients with normal QTc, we went about analyzing if the maximum QTc on Holter added diagnostic value in this target population of probands with suspected LQTS. In the entire cohort of 214 patients in this study, high SS had a sensitivity of 83% and specificity of 79% in identifying mutation carriers; in the group of patients with low/intermediate SS, prolonged resting QTc had a sensitivity of 56% and specificity of 76% in detecting mutation carriers; and in the most challenging group of patients with low/intermediate SS and normal resting QTc, prolonged QTc on Holter was 100% sensitive and 22% specific in detecting genotype-positivity. The value of the Holter QTc therefore potentially lies in ruling-out LQTS in probands with low to intermediate SS and normal range resting QTc; however, due to a high number of false positives, prolonged QTc on Holter by itself does not seem to be effective in predicting genotype-positivity. Not unexpectedly, incidental observation of prolonged QTc in asymptomatic individuals yielded only 8% positivity on genetic testing, in this cohort.

This study is limited by its retrospective nature and also by the relatively small number of subjects in the low/intermediate SS group. However, the study findings are clinically relevant and have practical implications in situations where genetic testing

<table>
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<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
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<tr>
<td>Schwartz score 3.5 (n=214)</td>
<td>83 (74-90)</td>
<td>79 (70-85)</td>
</tr>
<tr>
<td>QTc &gt;450 ms when SS ≤3 (n=111)</td>
<td>56 (31-79)</td>
<td>76 (66-84)</td>
</tr>
<tr>
<td>QTcH &gt;450 ms when SS ≤3 and QTc ≤450 ms (n=79)</td>
<td>100 (56-100)</td>
<td>22 (14-34)</td>
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</table>
is not readily available. Though analysis of exercise tests was not part of this study, it is tempting to believe that a combination of the previously proposed exercise-based algorithm\(^9\) and maximum QTc on Holter would help demarcate accurately the mutation carriers from the genotype-negative patients. In very young children who are typically not suitable for exercise testing, the chance of genotype-positivity may be assessed using resting QTc and Holter QTc. As our study focussed only on the maximum Holter QTc, we are unable to comment on the diagnostic utility of abnormal rhythm detected in the Holter test.\(^{10}\)

**Conclusions**

Genetic testing is clearly the cornerstone in diagnosing LQTS but it is still not uniformly available to all patients and also calls for prudent usage due to the associated high costs and often inconclusive results. In patients with a questionable phenotype and a nondiagnostic resting QTc, Holter QTc cut-off of 450 ms is highly effective in ruling-out LQTS.

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**Figure 2.** Correlation of maximum Holter QTc (QTcH, mean ± SD) with mutation carri ership in patients with Schwartz score ≤3 and normal resting QTc.
References


