Prolonged QT Syndromes: Congenital and Acquired

April 30, 2014
Elizabeth S. Kaufman, MD

I have no financial disclosures.
Prolonged QT Syndromes

• Congenital LQTS
  – Genetic basis
  – Diagnosis
  – Risk assessment
  – Treatment
  – Role of genetic testing

• Acquired LQTS
  – Risk factors for torsades
  – Medications that prolong QT
  – How to keep patients safe
Congenital Long QT Syndrome

- Genetic disorder (autosomal dominant)
- QT interval prolonged
  - >440 ms in males
  - >460 ms in females
- Torsades de pointes VT
- Syncope and sudden cardiac death
- Congenital deafness in Jervell and Lange-Nielsen syndrome (autosomal recessive)
Holter ECG Recording in LQTS Patient with Syncope (representative strips of ECG recording, part 1 of 2)

From Moss AJ with the C.A.R.E. Foundation, 2002
Holter ECG Recording in LQTS Patient with Syncope
(representative strips of ECG recording, part 2 of 2)

From Moss AJ with the C.A.R.E. Foundation, 2002
Measuring QT: Tangent Method

Postema et al. Heart Rhythm 2008;5:1015-1018
Basis for the Long QT Syndrome

Modified from JCE 1999;10:1664-1683
# Genetic Basis for Congenital LQTS

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<td>LQT4</td>
<td>4q25</td>
<td>ANK2</td>
<td>Ankyrin-B</td>
<td>$I_{Na,K}\downarrow I_{NCX}\downarrow$</td>
<td>rare</td>
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<td>LQT6</td>
<td>21q22.1</td>
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<td>LQT7*</td>
<td>17q23</td>
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<td>rare</td>
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<td>LQT8**</td>
<td>12p13.3</td>
<td>CACNA1C</td>
<td>$Ca_V1.2\alpha_{1c}$</td>
<td>$I_{Ca,L}\uparrow$</td>
<td>rare</td>
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<td>LQT9</td>
<td>3p25</td>
<td>CAV3</td>
<td>Caveolin-3</td>
<td>$I_{Na}\uparrow$</td>
<td>rare</td>
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<td>11q23</td>
<td>SCN4B</td>
<td>$Na_V1.5\beta_{4}$</td>
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<td>$I_{Kach}\uparrow$</td>
<td>rare</td>
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T-wave Morphology in LQTS by Genotype

Occurrence of Gene-Specific Triggers

Schwartz et al. Circ 2001;103:89-95
Making the Diagnosis

![Bar graph showing QTc (s)]

Phenotype/Genotype Mismatch

- Genetic variations!
- Environmental factors
Phenotype-Genotype Mismatch

• Diagnostic Dilemma
  – Accurate diagnosis and treatment saves lives.
  – Even individuals with normal phenotype at baseline may be at risk for sudden death during adrenergic stimulation.

• Which patients should be treated, and how should they be treated?
Diagnosis

- ECG (QT interval) at baseline
- ECG with exercise, 24-hour monitor
- Symptoms
- Family history
- Genetic testing
Treatment Options

- Avoidance of QT-prolonging drugs
- Restriction from competitive sports
- Antiadrenergic therapy
  - >53% 15-year mortality for LQTS patients presenting with syncope
  - 9% after antiadrenergic therapy
    - (1985 Schwartz and Locati)
  - Choice of beta blocker matters!
- ICD
Which subgroups of LQTS patients are inadequately protected by beta blocker therapy?
Markers of High Risk

- Symptoms in the first year of life
- Aborted cardiac arrest
- Syncope (on beta-blockers)
- Excessive QT prolongation
- Gender, age
- LQTS genetic subtype
- Specific mutation
Excessive QT Prolongation and Syncope

Hobbs et al. for the International LQT Registry, JAMA 2006;296:1252
Age and Gender Interaction: Any symptom

Fig. 1A
Probability of a First Cardiac Event from age 1 through 75 years by Gender

![Graph showing the probability of a first cardiac event from age 1 to 75 years by gender.](image)

Unadjusted $P = 0.013$

Age 1–75

Female

Male

<table>
<thead>
<tr>
<th>Age</th>
<th>Female Patients at Risk</th>
<th>Male Patients at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2319 (0.22)</td>
<td>1450 (0.26)</td>
</tr>
<tr>
<td>6</td>
<td>1506 (0.36)</td>
<td>786 (0.31)</td>
</tr>
<tr>
<td>16</td>
<td>919 (0.42)</td>
<td>530 (0.34)</td>
</tr>
<tr>
<td>26</td>
<td>587 (0.48)</td>
<td>383 (0.36)</td>
</tr>
<tr>
<td>36</td>
<td>305 (0.56)</td>
<td>222 (0.38)</td>
</tr>
<tr>
<td>46</td>
<td>87 (0.61)</td>
<td>73 (0.41)</td>
</tr>
</tbody>
</table>

Courtesy of Ilan Goldenberg
LQT2: Cardiac Event Rate by Gender

Unadjusted $P < 0.001$

Cumulative Probability of Cardiac Event for Patients with LQT2

Age (Years)

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>161</td>
<td>221</td>
</tr>
<tr>
<td>10</td>
<td>129 (0.14)</td>
<td>166 (0.11)</td>
</tr>
<tr>
<td>20</td>
<td>86 (0.27)</td>
<td>111 (0.42)</td>
</tr>
<tr>
<td>30</td>
<td>72 (0.31)</td>
<td>69 (0.60)</td>
</tr>
<tr>
<td>40</td>
<td>53 (0.35)</td>
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Courtesy of Ilan Goldenberg
Residual Rate of First Cardiac Events during \(\beta\)-Blocker Therapy
Event-free survival on beta-blockers

Priori et al. JAMA 2004;292:1341-1344
Appropriate ICD shocks by history

Appropriate ICD shocks by QTc

Appropriate ICD shocks by genotype

LQT3 Dogma until recently

- Outcomes in LQT3 are unpredictable.
- No evident protective effect of beta blocker therapy in LQT3
- High-risk patients with LQT3 should receive an ICD.
LQT3, gain-of-function sodium channel mutation

5-10% of genotyped LQTS
403 Patients with 53 Different SCN5a Mutations
Gender and Risk in LQT3

Unadjusted P=0.20

Patients at Risk
Male 181 151 (0.09) 102 (0.25) 77 (0.33) 68 (0.33)
Female 222 196 (0.06) 122 (0.28) 95 (0.36) 69 (0.45)
QT interval and risk in LQT3

Unadjusted P=0.009

Patients at Risk

<table>
<thead>
<tr>
<th>QTc Group</th>
<th>Patients at Risk</th>
<th>Age 0-10</th>
<th>Age 11-20</th>
<th>Age 21-30</th>
<th>Age 31-40</th>
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<tr>
<td>QTc &lt; 460</td>
<td>115 (0.05)</td>
<td>79 (0.17)</td>
<td>61 (0.20)</td>
<td>47 (0.26)</td>
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<tr>
<td>QTc 460-499</td>
<td>100 (0.06)</td>
<td>56 (0.22)</td>
<td>45 (0.30)</td>
<td>41 (0.31)</td>
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<tr>
<td>QTc 460-530</td>
<td>63 (0.11)</td>
<td>36 (0.29)</td>
<td>29 (0.36)</td>
<td>24 (0.43)</td>
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<tr>
<td>QTc &gt; 530</td>
<td>57 (0.07)</td>
<td>28 (0.41)</td>
<td>21 (0.48)</td>
<td>16 (0.48)</td>
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QTc and risk of lethal event in LQT3

Unadjusted P<0.001

Patients at Risk
- QTc <460: 138 (119, 86, 67, 53)
- QTc 460-499: 100 (91, 68, 56, 49)
- QTc 500-530: 63 (59, 45, 36, 31)
- QTc >530: 57 (52, 33, 27, 16)
LQT3, Study of 403 Patients

- 130 (32%) had a first cardiac event, of which 40 were ACA/SCD
- Risk directly related to QT interval
- No gender difference in risk
- Higher risk in symptomatic patients
- Very high risk among those symptomatic during first year of life
- Beta blockers are protective!
Roles for Genetic Testing in LQTS

1. To stratify risk and guide therapy, by defining the subtype of LQTS

2. To make or exclude the diagnosis in a borderline-phenotype individual, when the family’s mutation is known
Case #1, Genetic testing

- 20-year-old male student presents with syncope.
- QTc interval is 0.50 seconds.
- Genetic testing is performed.
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Sensitivity about 70%
Example of Test Results

Class I: Disease-causing mutation
Class II: Possible disease-causing mutation
Class III: Unlikely to be disease-causing

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<tr>
<th>Num</th>
<th>Gene</th>
<th>Region(G)</th>
<th>Nucl.Change</th>
<th>A.A.Change</th>
<th>Genotype</th>
<th>Region(P)</th>
<th>Region Type(P)</th>
<th>Class</th>
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<tr>
<td>1</td>
<td>KCNQ1</td>
<td>exon 15</td>
<td>1760 C&gt;T</td>
<td>Thr 587 Met</td>
<td>C/T</td>
<td>C-Terminal</td>
<td>C-Terminal</td>
<td>II</td>
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<tr>
<td>2</td>
<td>KCNE1</td>
<td>exon 4</td>
<td>112 G&gt;A</td>
<td>Gly 38 Ser</td>
<td>A/A</td>
<td>N-Terminal</td>
<td>N-Terminal</td>
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**TEST RESULTS**

Possible Deleterious Mutation Detected

This individual is positive for a Class II mutation, which is likely associated with disease.
20-year-old male student presents with syncope.

QTc interval is 0.50 seconds.

Genetic testing reveals a LQT1 mutation.

Patient is treated with beta blocker therapy and modification of exercise.
Limitations of genetic testing

- In a normal/borderline phenotype individual, when a family’s mutation is not known,
  - Sensitivity low
  - Specificity low
- A genetic result must be interpreted in clinical context.
Roles for Genetic Testing in LQTS

1. To stratify risk and guide therapy, by defining the subtype of LQTS

2. To make or exclude the diagnosis in a borderline-phenotype individual, when the family’s mutation is known
Case 2: Genetic testing

- A 14-year-old girl wants to play on the school basketball team.
- Brother died suddenly while running and was found to have a LQT1 mutation.
- No syncope
- QTc 0.46 seconds
Making the Diagnosis

Gene-positive

• Avoidance of high-intensity sports?

• Beta blocker

• Surveillance, serial ECGs, exercise tests, Holters

Or not

• Can play sports

• No beta blocker

• No cardiologist
If positive, would she need an ICD?

- Probably not!
- Variable penetrance
- A positive genotype is only weakly predictive of risk and must be interpreted in the context of clinical risk markers.
Why make the diagnosis?

- Appropriate treatment saves lives.
- Avoiding inappropriate treatment saves money, quality of life.

Genetic testing can “rule in” or “rule out” the diagnosis, in a borderline-phenotype individual, when the family’s mutation is known.
Why is Sensitivity Low?

- We haven’t discovered other major ion channel genes(?)
- The genetic substrate for LQTS is more complex!
• Patients with abnormal genotype but normal phenotype may demonstrate LQTS with further provocation (drugs, electrolyte disorders, bradycardia).

• Patients with “acquired” LQTS when exposed to drugs, etc. might have underlying “silent” genetic mutation.
Acquired LQTS

- Small minority have underlying mutation in major LQTS genes.
- A disproportionately high number of ALQTS patients have certain “benign” LQTS polymorphisms.
Implications

- Genotype (or our current understanding of it) incompletely predicts phenotype
- Clinical risk stratification still essential for guiding therapy.
Risk Factors for Torsades

- Female gender
- Age over 65 years
- Bradycardia
- Low K, Mg or diuretic use
- Structural heart disease (HF, LVH)
- Multiple drugs
- Genetic polymorphisms
- Prolonged baseline QT
Most torsades de pointes is seen with QTc $\geq 0.50$ seconds.
Electrolytes: Potassium

Compton, Circulation 1996
QT-Prolonging Drugs

- Antiarrhythmics
- Antihistamines
- Antimicrobials
- Antifungals
- Antipsychotics
- Antidepressants
Miscellaneous Drugs to Avoid

- Epinephrine
- Diuretics
- Probucol
- Cisapride

- Ephedra*
- Ma huang*
- Chloral hydrate
- Methadone
Inhibitors of CYP3A4

- Imidazole antifungals
- Macrolide antibiotics
- Cimetidine
- Fluoxetine
- Paroxetine
- Haloperidol
- Grapefruit juice
My guidelines

QTc > .44 seconds → ? initiation

QTc > .50 seconds on drug → ? stop drug, intensify monitoring

QT > 0.55 seconds → Stop, ? admit

Torsades or syncope → Admit, stop drug, monitor
Summary

- Risk factors for life-threatening torsades de pointes can be identified.
- Avoid multiple drugs
- Replace electrolytes
- Continuous ECG monitoring of high-risk patients allows early recognition and treatment of serious arrhythmias.
CLOSE TO HOME
By John McPherson

“Hey, Lor! Take a look at Mr. Geckler’s EKG!”