The Congenital Long QT Syndrome
Paul Sansone, M.D.

Objectives
- Review based on current literature
- Personal account
  - Help bridge the gap from bench to bedside
- Promote early diagnosis
  - Recognizing signs and symptoms
  - Characteristic ECG findings
  - Family history

Significant Advancements
- Diagnosis
- Genetics
- Diversity of presentation
- Molecular and cellular pathophysiology
- Risk stratification
- Treatment

Inherited Arrhythmia Syndromes
“Cardiac Ion Channelopathies”
- Long QT Syndrome
- Short QT Syndrome
- Catecholaminergic Polymorphic VT
- Brugada Syndrome
- Progressive Cardiac Conduction Defect
- Familial Syndromes
  - Sick Sinus Syndrome
  - Wolff-Parkinson-White
  - Atrial Fibrillation

Congenital LQTS
- Clinical syndrome of genetic origin
- Characterized by prolongation of QT interval on the ECG in the majority of cases
- Development of lethal arrhythmias caused by the polymorphic VT known as Torsades de Pointes

Cause For Concern
- Likely higher prevalence than reported
  - Italian neonatal ECG screening data
  - Probands with compound mutations
- Genetic testing
  - 2004 became commercially available
  - Normal/borderline QT interval patients
- SIDS association
- Sudden Unexplained Death Syndrome data
- Effective therapies
1856
- Report of the sudden death of a deaf girl while being reprimanded at school

1939
- Family with a consanguineous marriage reported in which all five children were deaf and suffered ‘epileptic spells.’
- One child suffered a sudden death

1957: Jervell and Lange-Nielsen
- First complete description
- Four children with congenital deaf-mutism
- Episodes of syncope
- QT interval prolonged
- 3 died suddenly
- Pattern suggestive of autosomal recessive inheritance

1963 Romano and 1964 Ward
- Independently described almost identical disorder
- Again syncopal episodes and QT interval prolonged
- TdP and Vfib documented
- Pattern suggestive of autosomal dominance
- Introduction of ICI45,520 (Inderal)

More History
- 1966 Yanowitz
  - Production of Neurogenic ECG Changes By Unilateral Alteration of Sympathetic Tone
- First successful left cardiac sympathetic denervations (LCSD)
  - 1971 Moss et al.
  - 1973 Schwartz et al.
- 1979 International Long QT Syndrome Registry

The Major Breakthrough
- 1991 Keating et al.
  - Demonstrated linkage of congenital LQTS to Harvey ras-1 locus on chromosome 11
- March of 1995 to January 1996
  - Successful identification of three LQTS genes
  - Dispelled previous theories on mechanism
  - “Sympathetic Imbalance” hypothesis
LQTS: Molecular Genetics Era

- Genotype
  - Type and location of genetic mutation
- Phenotype
  - ECG: QT interval, T wave morphology
  - Clinical: triggers; response to therapies
- Risk stratification
- Variable penetrance: ‘modifier genes’
- Gene specific therapy

Genetic and Cellular Mechanisms

- Reduced slowly activating delayed rectifier K+ current
- Decreased rapidly activating K+ current
- Decreased inwardly rectifying K+ current
- Increased inwardly rectifying K+ current
- Increased L-type calcium current

LQTS Genes

- Eight genes and over 300 mutations
- LQT1 (~50%), LQT2 (35-40%), and LQT3 (~10%) account for 95% of mutations
- 5.4% of suspected LQTS patients with two mutations in LQTS genes
- 50-60% of LQTS patients with known mutation
Ventricular Action Potential

**Molecular Contribution**
- Loss of function
  - Potassium channels
- Gain of function
  - Sodium, calcium channels
- Type and location of mutation
  - Dominant-negative effect (>50% reduction)
  - Haploinsufficiency (<50% reduction)

**Cellular Basis**
- Regional heterogeneity in action potential duration across ventricular myocardium
- Transmural Dispersion of Repolarization
  - Difference in repolarization time between endocardial, epicardial and M cell types

**Cellular Mechanisms**
- Mechanism Underlying TdP
  - Reentry
    - Increase in TDR creates vulnerable window
    - Believed responsible for maintenance of TdP
  - Triggered activity
    - Early afterdepolarizations (EADs)- M cells
    - Delayed afterdepolarizations (DADs)
    - Responsible for initiation of TdP
  - Sudden acceleration from slow HR
    - Highest risk for development of TdP
    - Prior emphasis on short-long-short cycle length
Clinical Presentation

- Sudden death
- Syncope (more common)
  - Aborted cardiac arrest (less common)
- Prolonged QT interval
- Incidental finding on ECG for other reason
- Preparticipation athletic screening

Diagnosis

- Syncope (or ACA) + long QT = LQTS
  - Especially with exertion or emotional distress
- Asymptomatic patients with borderline QT
  - Exercise testing/epinephrine challenge
  - Holter monitoring
  - Serial ECGs
- Family history
  - Sudden death, drowning, SIDS, SUDS
- Mistaken for epilepsy and hysterical reaction

Normal Values of the QT Interval

- Older studies: Prolonged QTc > 440 msec
- Moss
  - Adult males: QTc > 450; borderline 430-450
  - Adult females: QTc > 470; borderline 450-470
  - Age < 15: QTc > 460; borderline 440-460
- Keating criteria
  - Males: QTc > 470; uncertain 450-460
  - Females: QTc > 480; uncertain 460-470

1993 LQTS Diagnostic Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
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<tbody>
<tr>
<td>QTc &gt; 440 ms</td>
<td>1</td>
</tr>
<tr>
<td>QTc &gt; 450 ms</td>
<td>2</td>
</tr>
<tr>
<td>QTc &gt; 470 ms</td>
<td>1</td>
</tr>
<tr>
<td>Family history</td>
<td>2</td>
</tr>
<tr>
<td>Sudden death in 1st degree</td>
<td>1</td>
</tr>
<tr>
<td>Low heart rate for age</td>
<td>0.5</td>
</tr>
</tbody>
</table>

QTc = QT/√RR (Bazett’s formula)

Clinical Presentation

- Family history
  - Sudden death, drowning, SIDS, SUDS
  - Mistaken for epilepsy and hysterical reaction

Genetic Testing

- Indicated for the proband
- Indicated in family members of proband
  - Significant variation in ECG/clinical penetrance
- Considered in borderline LQTS patients with:
  - Unexplained, exertional syncope
  - Drug-induced QT prolongation/TdP
  - High sensitivity and specificity
- Variants: potential for false positives
- Genetic Information Nondiscrimination Act
  - (GINA) finally passed
Genotype-Phenotype Correlations

Gene Specific Triggers
- LQT1 mostly exercise
- LQT2 mixed pattern
- Auditory very common in LQT2
- LQT3 majority during sleep/rest

Triggers for Lethal Events
- Similar pattern to that for all cardiac events
- Differences accentuated between LQT1 vs. LQT2/LQT3

Unusual Triggers
- Swimming very specific for LQT1
- Postpartum period (9 months) specific for LQT2
- Exertion (LQT1) and Auditory (LQT2) as previously described

Risk Stratification
QTc ≥ 500

"If I were you, and I’m not, I’d pass."

Reported Risk Factors

- QTc duration
- History of cardiac events
  - Aborted cardiac arrest (ACA)
  - Prior syncope
- Gender
- Genotype
- Family history
- Use of β-blockers

Risk Stratification in LQTS

- Priori et al. NEJM 2003
- QTc ≥ 500 single most important predictor
- QTc ≤ 446, 15% had events before age 40
- All comers: sex made no difference
- Among the genotypes
  - Female, LQT2 significantly higher risk
  - Males, LQT3 also higher risk (small numbers)
- Normal QTc: 36% LQT1, 19% LQT2, 10% LQT3

Risk Stratification: Major Publications

- Risk of ACA or SCD During Adolescence in the LQTS. JAMA. September 2006.

Influence of Genotype on Clinical Course

- Moss et al. NEJM 1998
- QTc ≥ 500 higher risk for events (again)
- LQT1 highest risk for events, then LQT2
  - LQT3 significantly lower event rate
- LQT3 with significantly higher percentage of lethal cardiac events
- Fewer families than the Priori study
  - 38 vs. 193

Therapy
Therapy for LQTS
- β-blockers
- Implantable Cardioverter-Defibrillators
- Left Cardiac Sympathetic Denervation
- Pacemakers
- Gene-specific therapy

β-Blockers
- Priori et al. 2004 JAMA
  - 336 genotype patients on β-blockers 5 years
  - Incidence of cardiac events not equal
    - LQT1 lowest (10%), followed by LQT2 (23%), then LQT3 (32%)
  - Other predictors included
    - QTc ≥ 500
      - First cardiac event in early childhood (≤ 7 yrs)
    - 47% of patients symptomatic pretreatment

More Data on β-Blockers
  - Effectiveness and limitations of β-blockers
  - 869 patients (139 genotype positive)
  - 69% of patients symptomatic pretreatment
  - Analysis of symptomatic vs. asymptomatic
  - Major risk factors:
    - β-blockers started at young age
    - Symptomatic before treatment
    - QTc not a significant risk factor

Risk Factors for Cardiac Events

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Any Cardiac Event</th>
<th>Aborted Cardiac Arrest or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (β-blocker started)</td>
<td></td>
<td></td>
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<tr>
<td>&lt;5 yrs</td>
<td>527</td>
<td>3.1 (0.3, 6.3)</td>
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<tr>
<td>5-14 yrs</td>
<td>560</td>
<td>1.6 (0.2, 8.1)</td>
</tr>
<tr>
<td>&gt;14 yrs</td>
<td>875</td>
<td>1.0</td>
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<tr>
<td>Sympathetic blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>271</td>
<td>1.0</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>560</td>
<td>1.6 (0.2, 8.1)</td>
</tr>
<tr>
<td>Syncope only</td>
<td>405</td>
<td>0.9</td>
</tr>
<tr>
<td>None</td>
<td>155</td>
<td>1.1</td>
</tr>
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</table>

Other variables without significant contribution to either model included: hospital/ambulatory beta-blocker status, sex, unipolar ventricular, gender, onset risk, other therapy, and family history of LQT3-related death. Patients were evaluated on β-blockers until 2 days after syncopal event. All patients died of cardiac arrest or death.

β-Blockers Summary
- Overall significant reduction in event rate
  - Overall mortality 2% treated patients
- LQT1 and LQT2 patients benefit the most
  - LQT3 patients limited benefit
- Symptomatic patients pretreatment higher risk (32% within 5 years)
- QTc ≥ 500 considered major risk factor
- Young age (symptoms/therapy) high risk
- Nadolol, Propranolol β-blockers of choice

Implantable Cardioverter Defibrillators
- Compelling evidence; nothing conclusive
- Typically reserved for higher risk patients
  - Aborted cardiac arrest
    - Syncope episodes while on β-blockers
- Influence of family history
- Medicolegal
  - Implants more common in U.S. vs. Europe
- Complications
ICD Data

- 2003 Zareba et al. largest experience
- 125 patients (73 high risk) with ICDs
- Control group 161 patients without ICD
  - Same high risk profile
- Results
  - ICD group: 1 death (1.3%), 6 year old GA
  - Non-ICD group: 26 deaths (16%)
- \( P = 0.07 \)

ICD Complications

- Implantation procedure related
  - Infections*, venous occlusion*, hematoma, seroma, lead dislodgement
- ICD system related complications
  - Inappropriate shocks* (SVT, T-wave over sense, lead failure), multiple shocks (VT/VF storm), lead failure*, need for generator replacement (recalls), increase in defibrillation thresholds*
- Psychological impact/adjustment
  - *higher in pediatric population

Guidelines for LQTS Management

*Data are from the American College of Cardiology, the American Heart Association, and the European Society of Cardiology, in collaboration with the European Society for Medical Hypertension Research and the Joint North European Group on Hypertension Research. Guidelines are adapted from Zipes et al. (2002).

Levels of recommendation as follows: 1, strong; 2, moderate; 3, weak. In order to provide a structured approach to therapeutic, practical, and ethical 4, conditions which make it part of a model in which risk is not used as a measure in the presence of a patient with a high risk of sudden death due to a channelopathy. \( ^* \) indicates a high risk of sudden death.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Land of Evidence</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No participation in competitive sports</td>
<td>1</td>
<td>Indicate patients with the diagnosis established by means of genetic testing only</td>
</tr>
<tr>
<td>No beta-blockers</td>
<td>1</td>
<td>For patients with a normal QT interval</td>
</tr>
<tr>
<td></td>
<td>2a</td>
<td>For patients with a normal QT interval</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>For patients with a prolonged QT interval</td>
</tr>
<tr>
<td></td>
<td>2c</td>
<td>For patients with a prolonged QT interval</td>
</tr>
</tbody>
</table>

Left Cardiac Sympathetic Denervation (LCSD)

- Involves resection of left SG (lower half) and first 4-5 thoracic ganglia
- Reserved for high risk patients
  - Adjunctive therapy with ICD and \( \beta \)-blockers
  - Reduces frequency of inappropriate shocks
  - Mechanism involves reduced NE release
  - Increases defibrillation threshold
- 2004 Schwartz et al. Circulation
  - Significant event reduction in high risk patients

Pacemakers

- Used in pause-dependent TdP
  - Typically LQT2 and LQT3
- Allows for full dose \( \beta \)-blockade
- Limited role as ICD technology advances
- Fast (overdrive) pacing function
  - May reduce shocks from electrical storm
- Never used as sole therapy

Gene-Specific Therapy: Behavioral Modifications

- Restriction in athletic participation
  - Controversy with LQTS patients
- LQT1: swimming
  - Syncopal episodes result in drowning
- LQT2: auditory triggers (startle response)
  - Alarm clocks, telephones, doorbells, fire alarms
- LQT3: episodes during rest/sleep
  - Use of intercom; shared bedroom
Gene-Specific Therapy: Targeted Treatments

- **Potassium control**
  - High [K+] increases \( I_{\text{Kr}} \) channel conductance
  - May compensate for current loss in KCNH2

- **Rescue of defective trafficking in KCNQ1**
  - Some success with astemizole, cisapride
  - Unfortunately, compounds are \( I_{\text{Kr}} \) blockers

- **Sodium channel: SCN5A mutations**
  - Mexiletine blocks late \( I_{\text{Na}} \), shortens QT interval
  - Some favorable preliminary data in LQT3
  - Other sodium channel blockers (flecainide)

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**Sudden Cardiac Arrest and the Sansone Family**

Paul Sansone, M.D.

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**Sansone Family Tree & Long QT**

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Finally...

The AED

Don't leave home without it
Pioneers

Peter J. Schwartz, M.D.

Arthur J. Moss, M.D.

Silvia G. Priori, M.D.