Management of Arrhythmia Syndromes in the Newborn and Very Young Child: Unique Risks & Barriers in this Age Population

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Disclosures: None
Channelopathies in the Young

- Long QT Syndrome
- Catecholamine Polymorphic VT
- Brugada Syndrome
- Short QT
Arrhythmia Syndromes in the VERY Young

- Challenges in diagnosing channelopathy conditions in newborns
- Management of neonatal channelopathies is a serious problem
- Generates major anxiety to families and physicians
- Treatment ranges from conservative management to more aggressive and invasive approaches
LONG QT SYNDROME
Diagnosing LQT is easy, when..
Challenges in Diagnosing LQTS

- Electrocardiogram Variability
  - 30% of patients with gene-positive LQT mutations have a QTc that overlaps normal healthy children.
  - 10-15% of healthy individuals have a QTc above a value of 440 msec
  - **Difficult to make EKG diagnosis before DOL #4**

A QTc >500 msec diagnosis is easy, the challenges often occur in the QTc 460-480 msec > moving beyond the EKG
Challenges in Diagnosing LQTS

• **Disease Variability**
  - Approximately 30% of patients with LQT mutations will never have a symptom.
  - Clinical signs, symptoms, and ECG characteristics do not adequately differentiate subtypes of LQTS.
  - Differentiating LQTS subtype may help risk prediction & aid in treatment options.
genotype patients ≈ 75%
Clinical Implications for Patients With Long QT Syndrome Who Experience a Cardiac Event During Infancy

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Pavia and Milan, Italy; Rochester, New York; Rochester, Minnesota; Jerusalem, Israel; Cleveland and Cincinnati, Ohio; and Salt Lake City, Utah
3,323 Infants with LQT in the 1st year of life

- SCD (20)
  - 8 F
  - All had QTc ≥ 500
  - 4/20 had an earlier event
- Aborted Cardiac Event (16)
  - 2.3 x risk of ACA/SCD between 1-10 year of age
- Syncope (34)
  - Not associated with ACA/LQT related SCD
  - Syncope within last 2 years and a QTc ≥ 500 increased risk SCD
- No LQT symptoms within 1st Yr (3,253)

Beta-blockers risk reduction of >65% in this sub-cohort
Beta-blockers should be first line of therapy
Beta blockers are not ALWAYS effective in the young
Cumulative Probability of ACA/LQT Related Death

QTc >500, female sex, HR < 100
predictors of cardiac events
Infants are Unique

- Children are not small adults
- Infants are not small children

- Symptomatic infants with LQT are HIGH RISK
- Tend to be sicker and can’t vocalize symptoms
- Beta-blockers are not uniformly 100% protective
- ICDs are a challenge to implant
- LCSD may be reasonable, but the infant is in a state of rapidly evolving autonomic development
  - (sleep cycle, sleep position, baroreceptors)
Scenario #1: My Pragmatic Approach to Diagnosing and Managing LQT in the Young Child

A parent has a known LQT diagnosis (genotype known)

Any fetal issues
VT?
Bradycardia?

YES
Assume same diagnosis

Management Based on Clinical Situation

AWAITING GENETIC TESTING CONFIRMATION

YES
Scenario #1: My Pragmatic Approach to Diagnosing and Managing LQT in the Young Child

A parent has a known LQT diagnosis (genotype known)

Any fetal issues VT? Bradycardia?

YES

Assume same diagnosis

NO

ECG Telemetry Holter (All Normal)

Management Based on Clinical Situation

Genetic Testing (cascade testing pending)

Close Observation (Don’t rush discharge)

Frequent Follow-Up (syncope awareness)

Avoid QT prolonging medications

AWAITING GENETIC TESTING
The Nursery “stable management” – Anticipatory Questions & Guidance

- What is the QT interval?
- What is the heart rate?
- Is the patient having any significant bradycardia?
- Is the patient having any ventricular arrhythmias?
- How long to watch in the nursery/NICU?
- What is the disposition (how far do they live)?
- What medications to start?
- CPR training for the parents?
- Who will be giving the meds?
- Dose adjustment for weight gain?
- How is the baby feeding (breast?)
- Medications to avoid
- What to tell the pediatrician
Scenario #1: My Pragmatic Approach to Diagnosing and Managing LQT in the Young Child

A parent has a known LQT diagnosis (genotype known)

Any fetal issues VT? Bradycardia?

ECG Telemetry Holter Abnormal Findings

Management Based on Clinical Situation

AWAITING GENETIC TESTING

• Beta-blockers
• Pacemaker
• ICD
• LCSD
• Lido/Mexilitine
• Magnesium
• Observation

NO
Scenario #2: My Pragmatic Approach to Diagnosing and Managing LQT in the Young Child

No concerning family history of a channelopathy

ECG obtained for incidental reasons
* patient is completely asymptomatic

No concerning family history of a channelopathy

QT Prolongation (<480)

QT Prolongation (>480)

QT Prolongation (>550)

Close Observation
Genetic Testing
Avoid QT ↑ meds
Frequent Follow-up

 +/- Beta-blockers

Frequent Follow-up

Beta-blockers

Won’t be asymptomatic for long
Manage accordingly
Scenario #3: My Pragmatic Approach to Diagnosing and Managing LQT in the Young Child

- No concerning family history of a channelopathy
- Normal fetal course
- ECG obtained because someone noticed: Bradycardia, AV block, Non-sustained VT

QT prolonged, Bizarre T waves, Non-sustained VT (Tdp)

- Beta-blockers
- Pacemaker
- ICD
- Left cardiac sympathetic denervation
- Lido/Mexilitine
- Magnesium
Don’t Forget to Do a Physical Exam

**Timothy Syndrome**

- Spontaneous mutation in CACNA1C.
- QT prolongation
- Fingers and toes syndactyly
- Thin upper lip
- Autism, developmental delay
Occurrence of Gene-Specific Triggers

<table>
<thead>
<tr>
<th>Gene</th>
<th>EXERCISE</th>
<th>EMOTION</th>
<th>REST</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT 1</td>
<td>60%</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>LQT 2</td>
<td>50%</td>
<td>40%</td>
<td>10%</td>
</tr>
<tr>
<td>LQT 3</td>
<td>40%</td>
<td>30%</td>
<td>30%</td>
</tr>
</tbody>
</table>
Emotion  No Sleep  Stress

Do Not Forget Mom in Hereditary LQT
Approach to the Asymptomatic Young Patient with LQT

![Graph showing the percentage of patients with cardiac events before and after β-blocker treatment.](image)

- **Before β-Blocker** vs **After β-Blocker**
- **LQT1 (n=69)**: 57% vs 19%
- **LQT2 (n=42)**: 57% vs 36%
- **LQT3 (n=28)**: 14% vs 14%

Significance levels:
- **P<0.001**
- **NS** (Not Significant)

Subjects from the International LQTS Registry
Not All Beta-Blockers Are Equal

Efficacy of Different Beta-Blockers in the Treatment of Long QT Syndrome

Abeer Abu-Zeitone, BS PHARM, MS, PhD, Derick R. Peterson, PhD, Bronislava Polonsky, MS, Scott McNitt, MS, Arthur J. Moss, MD

ABSTRACT

BACKGROUND In LQTS, β-blocker therapy is effective in reducing the risk of cardiac events (syncope, aborted cardiac arrest, sudden cardiac death). Limited studies have compared the efficacy of different β-blockers.

OBJECTIVES The goal of this study was to compare the efficacy of different β-blockers in long QT syndrome (LQTS) and in genotype-positive patients with LQT1 and LQT2.

METHODS The study included 1,530 patients from the Rochester, New York-based LQTS Registry who were prescribed β-blockers and were followed for 5 years.

CONCLUSIONS Although the 4 β-blockers are equally effective in reducing the risk of first cardiac event, their efficacy differed by genotype; nadolol was the only β-blocker associated with a significant risk reduction in patients with LQT2. Patients experiencing cardiac events during β-blocker therapy are at high risk for subsequent cardiac events, and propranolol is the least effective drug in this high-risk group.

LQT2: Nadolol only BB significant risk-reduction in 1st cardiac event
LQT1: no difference in 1st-cardiac event amongst 4 BB
Propanolol the least effective against recurrent cardiac events
Not All Beta-Blockers Are Equal

Nadolol, Metoprolol, Propanolol

Evaluated only LQT 1 & 2 Patients
Excluded anyone on BB < 1 year of age
Propanolol had the greatest effect on QTc shortening
Propanolol & Nadolol equally effective
Metoprolol should NOT be used for symptomatic LQT 1 or LQT 2
Management: Drug Avoidance in Long QT

- **AVOID**: Certain drugs may provoke life-threatening arrhythmias in patients with LQT (www.QTdrugs.org)
  - **Anti-arrhythmics**
    - procainamide, amiodarone, sotalol
  - **Anti-histamine**
    - astemizole, terfenedine
  - **Anti-fungal & anti-microbial**
    - ketoconazole
    - trimethoprim/sulfa
  - **Psychotropic medications**
    - haloperidol, tricyclics
- Avoid nonessential OTC medications in LQT
Long QT3 (gain function Na channel)

- Most of what we have talked about regarding BB has related to LQT 1 & 2.
- **Long QT is NOT one disease entity**
- Genotype & phenotype differences (age/sex)
- Tends to cause more bradycardia, BB OK?

- Multicenter Study: 406 LQT3 pts ([Wilde A Circ 2016](#))
- Followed LQT3 patients after 1 year
- 12 patients symptomatic in 1st year-of-life
  - 7 syncope
  - 6 had ACA (4 died)

**Symptomatic LQT3 in year 1 very concerning**
Approach to the Symptomatic Young Patient with LQT

Are we dealing with bradycardia?
- Sinus bradycardia?
- 2:1 AV block?

Are we dealing with VT?
- Pause-dependent?

How bad is the QT?
- $>500$ msec?
- $>600$ msec?
Challenging Case #1

Term newborn at 48 hours noted to have bradycardia (85 bpm) and some respiratory distress. Also noted by the OB to have some bradycardia at 30 weeks gestation.

- No family history of syncope or SCD

![ECG Image]

- Normal ECHO
- QTc 730 msec
- Occasional single PVCs

*Courtesy Roman Gebauer*
ECG in age of 2 days
30 minute after arrival in ICU

Defibrillation
Intubation
Chest compressions (brief)
Options

- Beta-blockers
- Mexilitine
- Beta-blockers and Mexilitine
- Beta-blockers and pacemaker
- Pacemaker only
- Left sympathetic denervation
- ICD
- Combination of the above
- All of the above
Clinical Course

- IV beta-blockers (Esmolol 100ug/kg/min)
- No further episodes of TdP
- IV lidocaine given (? shortening of QT)
- Suspicious this was LQT 3
- Mexiltine added to propanolol
Follow-Up EKG – SCN5A 9c.5314C>G

QTc 480-580 msec

Stayed in hospital for 1 month
No further episodes
Doing well
Challenging Case #2

- Called from a remote clinic with a 37 week 2.7 kg baby born via emergent c/s secondary to bradycardia.

- Bradycardia lasted for about 90 min and now the HR has returned to 130 bpm (regular) and the neonate appears well with a normal cardiovascular examination.

- Baby is transferred to the NICU at the children’s hospital – clinically remains well - no further bradycardia over a period of 3 days
Electrocardiogram (immediately after birth)
- **Family History:** 2 older sisters both healthy, mom has a history of “vagal-like” events a number of years ago and a seizure when she was 16. No other family history of syncope, seizures, sudden cardiac death.

- **Physical Examination:** 2.7 kg, HR 138, BP 62/38
  - Normal examination

- **Echocardiogram:** structurally normal heart; excellent bi-ventricular function.

- **Laboratory Studies:**
  - Electrolytes Normal
While getting a rhythm strip....
D.O.L #4 while on telemetry.....

that was it – never happened again
Heart rate maybe a little slower,
but not necessarily true pause-dependent TdP
Started IV Esmolol
Electrocardiogram (DOL #5)
Options

☐ Beta-blockers
☐ Beta-blockers and Mexilitine
☐ Beta-blockers and pacemaker
☐ Pacemaker only
☐ Left sympathetic denervation
☐ ICD
☐ Combination of the above
☐ All of the above
☐ Pray your week of service ends today
Options

- Beta-blockers
- Beta-blockers and Mexilitine
- **Beta-blockers and pacemaker**
- Pacemaker only
- **Left sympathetic denervation**
- ICD
- Combination of the above
- All of the above
- Pray your week of service ends today
Gene Test: KCNH2 (LQT 2)

- Continue on propanolol 4mg/kg/day
- Left AAI paced at 80-90 bpm
- At age 4 years (still asymptomatic) routine interrogation of her PM early ventricular couplets noted.
- Underwent PM removal, addition of an epicardial coil, ICD system
- Changed to nadolol
- No events in the last year
Long QT with 2:1 AV block is rare
4.5% of congenital LQT diagnosis
12 patients diagnosed DOL #1 (QTc range 531-840 msec)
N=8 (67%) received a permanent pacemaker
N=3 (25%) received ICD for TdP while on beta-blockers
No mortality
QTc shortens overtime even in initially high-risk patients
Can we go from Sudden Cardiac Death to Sudden Infant Death?
Despite the drastic reduction still the 3rd most common cause of infant mortality in the US.
Sudden Infant Death Syndrome and Long QT Syndrome

Zealots

Naysayers
Physiological Factors

Quiet sleep prolongs the QT interval

*Pediatr Res* 1979;13:139-41

Effect of Position on Sleep, Heart Rate Variability, and QT Interval in Preterm Infants at 1 and 3 Months’ Corrected Age

Ronald L. Ariagno, MD*, Majid Mirmiran, MD*§, Marian M. Adams, MD*, Anna G. Saporito, MS*, Anne M. Dubin, MD†, Roger B. Baldwin, MA*

**TABLE 4.** QT and JT Intervals Compared With Sleep Position

<table>
<thead>
<tr>
<th></th>
<th>QTc average, 5 hr</th>
<th>JTc average, 5 hr</th>
<th>1 mo</th>
<th>3 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc average, 1 mo</td>
<td>0.511 (0.019)</td>
<td>0.514 (0.019)</td>
<td>0.451 (0.023)</td>
<td>0.443 (0.025)</td>
</tr>
<tr>
<td>QTc average, 3 mo</td>
<td>0.418 (0.019)</td>
<td>0.422 (0.018)</td>
<td>0.418 (0.019)</td>
<td>0.422 (0.018)</td>
</tr>
</tbody>
</table>

QTc significantly shortens during quiet sleep supine but not prone
Peak Incidence SIDS @2-3 months

QT INTERVAL IN HEALTHY INFANTS

\[ QT_c = 397 \pm 18 \text{ msec} \]
\[ 409 \pm 15 \]
\[ 406 \pm 15 \]
\[ 400 \pm 14 \]

\( n = 3946, 2418, 351, 234 \)

\( p < 0.0001 \)

Circ 1982
Physical & Emotional Stress Can Prolong the QT
Clinical retrospective link between SIDS & LQT

Potential Role of QT Interval Prolongation in Sudden Infant Death Syndrome

Barry J. Maron, M.D., Chester E. Clark, M.D., Robert E. Goldstein, M.D., and Stephen E. Epstein, M.D.

- 42 sets of parents with at least one infant with SIDS
- QT prolongation was present in at least one member of 11 (26%).
- In families where a parent had prolongation of QT interval, 36% of siblings also had QT prolongation.
clinical prospective link between SIDS & LQT

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PROLONGATION OF THE QT INTERVAL AND THE SUDDEN INFANT DEATH SYNDROME

PETER JOHN SCHWARTZ, M.D., MARCO STRAMBA-BADIALE, M.D., PH.D., ALESSANDRO SEGANTINI, M.D., PAOLA AUXTONI, M.D., GIULIANO BOSI, M.D., ROBERTO GIORGETTI, M.D., FABIO GRANCINI, M.D., ERNESTO DIEGO MARINI, M.D., FRANCESCO PERTICONE, M.D., DARIO ROSTI, M.D., AND PATRIZIA SALICE, M.D.*
ODDS RATIO FOR SCD (QTc >440 msec)
Females: 33
Males: 47
Postmortem Molecular Analysis of SCN5A Defects in Sudden Infant Death Syndrome

Michael J. Ackerman, MD, PhD
Benjamin L. Siu, MD
William Q. Sturner, MD
David J. Tester, BS
Carmen R. Valdivia, MD

Context Fatal arrhythmias from occult long QT syndrome may be responsible for some cases of sudden infant death syndrome (SIDS). Because patients who have long QT syndrome with sodium channel gene (SCN5A) defects have an increased frequency of cardiac events during sleep, and a recent case is reported of a sporadic SCN5A mutation in an infant with near SIDS, SCN5A has emerged as the leading candidate ion channel gene for SIDS.

Objective To determine the prevalence and functional properties of SCN5A mutations.

Postmortem molecular analysis of 93 SIDS victims

- Searched for SCN5A ONLY
- 2 mutations
- 4 week-old and 6 week old
- SIDS attributable to 2% mutations in SCN5A
Guthrie Cards

Posthumous diagnosis of long QT syndrome from neonatal screening cards.

Gladding PA, Evans CA, Crawford J, Chung SK, Vaughan A, Webster D, Neas K, Love DR, Rees MI, Shelling AN, Skinner JR.
Cardiac Inherited Diseases Group, Auckland City Hospital/Starship Children's Hospital, Auckland, New Zealand.

Abstract

N=19 cases of SCD in New Zealand
6/19 (31%) identified as having a channelopathy
Sudden unexplained death in infants and children: the role of undiagnosed inherited cardiac conditions

Table 1  Genes with mutations associated with SIDS and SADS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Encoded protein</th>
<th>Frequency in SADS (%)</th>
<th>Frequency in SIDS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1</td>
<td>Kv7.1 potassium channel α-subunit</td>
<td>6.4^29</td>
<td>1.0^30–32</td>
</tr>
<tr>
<td>LQT2</td>
<td>KCNH2/HERG</td>
<td>Kv11.1 potassium channel α-subunit</td>
<td>3.5^29</td>
<td>0.5^30</td>
</tr>
<tr>
<td>LQT3/BrS1</td>
<td>SCN5A</td>
<td>Nav1.5 sodium channel α-subunit</td>
<td>3.5^29</td>
<td>4.8^30–34</td>
</tr>
<tr>
<td>LQT6</td>
<td>KCNE2</td>
<td>MiRP1 potassium channel β-subunit</td>
<td>1.2^29</td>
<td>0.5^30</td>
</tr>
<tr>
<td>LQT9</td>
<td>CAV3</td>
<td>Caveolin 3</td>
<td>1.5^30,35</td>
<td></td>
</tr>
<tr>
<td>LQT10</td>
<td>SCN4B</td>
<td>Navβ4 sodium channel β-subunit</td>
<td>0.3^36</td>
<td></td>
</tr>
<tr>
<td>LQT12</td>
<td>SNTA1</td>
<td>Alpha-1-syntrophin</td>
<td>1.0^37</td>
<td></td>
</tr>
<tr>
<td>CPVT1</td>
<td>RYR2</td>
<td>Cardiac ryanodine receptor</td>
<td>11.6^29</td>
<td>1.5^38</td>
</tr>
<tr>
<td>BrS2</td>
<td>GPD1-L</td>
<td>Glycerol-3-phosphate dehydrogenase 1-like sodium channel interacting protein</td>
<td></td>
<td>0.9^39</td>
</tr>
<tr>
<td>BrS7</td>
<td>SCN3B</td>
<td>Navβ3 sodium channel β-subunit</td>
<td>0.7^36</td>
<td></td>
</tr>
<tr>
<td>BrS8</td>
<td>KCNJ8</td>
<td>Kir6.1 potassium channel α-subunit</td>
<td>0.7^40</td>
<td></td>
</tr>
<tr>
<td>BrS2</td>
<td>GJA1</td>
<td>Cx43 gap junction protein</td>
<td>0.3^41</td>
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<tr>
<td>HCM</td>
<td>MYBPC3</td>
<td>Cardiac myosin-binding protein C</td>
<td>0.6^42</td>
<td></td>
</tr>
<tr>
<td>HCM</td>
<td>TNNI3</td>
<td>Cardiac troponin I</td>
<td>0.3^42</td>
<td></td>
</tr>
</tbody>
</table>
close to 1,000 molecular autopsy SIDS cases

- 1 in 5 SIDS victims carries a mutation of a cardiac related ion-channel gene defect
- Genetic analysis should be performed in cases of sudden infant death syndrome and sudden cardiac death