Electrical Abnormalities: Long QT and Beyond

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Genetic Electrical Myopathies “Channelopathies”

- Long QT Syndrome
- Short QT Syndrome
- Brugada Syndrome
- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)
Long QT Syndrome

- Prolongation of the QT interval associated with syncope, polymorphic VT (torsades de pointes) or sudden cardiac death (SCD).
- Heterogeneous disorder
  - Usually genetic disorder of either potassium or sodium ion channels
  - Can be acquired (medications, electrolytes, etc.)
- Incidence: ~1 in 3000

Cardiac events - syncope, cardiac arrest, or SCD - occur in approximately 1/3 of patients with known LQTS.

In patients with symptomatic, untreated LQTS, the mortality rate is as high as 20% for the first year and 50% at 10 years.


**Long QT Syndrome**


**Long QT Subtypes**

**Genetic Testing:** positive in 75%

<table>
<thead>
<tr>
<th>Subtype</th>
<th>%</th>
<th>Gene</th>
<th>Mutation</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long QT 1</td>
<td>42%</td>
<td>KCNQ1</td>
<td>K+ Channel mutation (IK(_Q))</td>
<td>Events with exercise / swimming</td>
</tr>
<tr>
<td>Long QT 2</td>
<td>45%</td>
<td>HERG</td>
<td>K+ Channel mutation (IK(_R))</td>
<td>Events with loud noises (IK(_R))</td>
</tr>
<tr>
<td>Long QT 3</td>
<td>8%</td>
<td>SCN5A</td>
<td>Na+ Channel mutation</td>
<td>Events during sleep</td>
</tr>
</tbody>
</table>

**SCN5A mutations**

- Gain of function causes long QT syndrome (LQT 3)
- Loss of function causes Brugada Syndrome

Others (9 other LQT variants) account for remaining 5% of positive gene tests

LQT Subtypes – ECG Manifestations

- Normal ECG
- Long QT 1: Wide-based T-wave
- Long QT 2: Notched T-wave
- Long QT 3: Late peaking T-wave after long isoelectric ST segment

Diagnosis?
What is a normal QTc?

**ECG findings**

- **QTc duration**
  - $\geq 480$ ms: 3 points
  - 460-470 ms: 2 points
  - $\geq 450$ ms (if male): 1 point
- **Torsade de points**: 2 points
- **T-Wave alternans**: 1 point
- **Notched T wave in three leads**: 1 point
- **Low heart rate for age (<2nd percentile)**: 0.5 point

**Clinical history:**

- **Syncope**
  - With stress: 2 points
  - Without stress: 1 point
- **Congenital deafness (Jervell and Lange-Nielsen Syndrome?)**: 0.5 point

**Family history:**

- **Family members with definite LQTS**: 1 point
- **Unexplained sudden cardiac death below age 30 among immediate family members**: 0.5 point

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**Long QT Syndrome**

Patients with 4 or more points are categorized as a high probability, 2-3 points as intermediate and one or less as low probability of having long QT syndrome.

Prognosis and Risk

- Mean age at first manifestation is 12 years.
- Longer QTc (>500 ms) more worrisome
- Family history of SCD not clearly related to risk of SCD
- LQT Subtype is important

LQT Risk Pyramid

Priori et al., N Engl J Med 2003, 348;19
Treatment – Beta Blockers

- Beta-blockers are the mainstay of therapy in LQTS

- Decreases risk for cardiac events
  - Can shorten QT interval by decreasing activation from the left stellate ganglion

Moss et al.:
- 869 LQTS patients treated with B-blockers
- Beta blockers reduced cardiac events from 0.97 to 0.31 per year


Treatment – Beta Blockers

Beta-Blockers work in LQT 1

- 216 long QT1 patients on beta blockers
- 157 (73%) with cardiac events prior to beta-blockers (syncope, CA, SCD)
- 75% asymptomatic after beta-blockers
- 12 cardiac arrests / SCD
  - 8 non-compliant
  - 2 QT-prolonging drugs
  - 1 both


Beta-blockers by LQT Subtype

Treatment - ICD

- Implantable Cardioverter Defibrillators (ICD)

- For high risk patients
  - Sudden cardiac arrest (secondary prevention)
  - LQT1 with syncope on beta-blockers
  - LQT2 with syncope
  - All LQT 3 patients

ICD outcomes in LQT

International Long QTS Registry


125 with ICD’s – 54 survivors of CA, 19 syncope on beta-blockers
161 controls without ICD’s – 89 survivors of CA, 72 syncope on beta-blockers
Treatment – Sympathectomy

- Left cardiac sympathetic denervation
  - Interrupts major source of norepinephrine to the heart via preganglionic denervation
  - Decreases cardiac adrenergic tone without decreasing heart rate
  - Resection of lower half of left stellate ganglion as well as second and third thoracic ganglia. Ocular fibers in upper half (lower risk of Horner’s syndrome)
  - Consider when:
    » Small size – difficult to place ICD
    » Asthma and cannot tolerate beta-blockers
    » ICD’s and frequent shocks
    » LQT3


Treatment – Sympathectomy

- Large study of 147 LQTS patients with sympathectomy
  - Event rate improved from 1.32 to 0.19 events per year
    » SCD or aborted CA from 0.13 to 0.06 events per year
  - In 5 patients with preoperative implantable defibrillator and multiple discharges, the post-LCSD count of shocks decreased by 95% (P = 0.02) from a median number of 25 to 0 per patient.
  - More useful in LQT1 and LQT3 than LQT2

Long QT Syndrome “Pearls”

- Comprehensive family history is imperative (syncope, seizures, SCD)
- Exercise test can be very useful for diagnosis
- Genetic testing should be considered
- Avoid QT prolonging drugs
- Exercise restriction generally advised
- Beta blockers mainstay of treatment – unless LQT 3
- Don’t forget sympathectomy

Genetic Electrical Myopathies

- Long QT Syndrome
- Short QT Syndrome
- Brugada Syndrome
- Catecholaminergic Polymorphic Ventricular Tachyardia (CPVT)
Short QT Syndrome

- Abnormally short QTc interval (<340 ms) and a propensity for atrial fibrillation and sudden cardiac death (SCD)

- Linked to mutations in several genes – all LQT genes encoding a different potassium ion channel involved in repolarization:
  - KCNQ1, HERG, KCNJ2

- Shortening of the effective refractory period combined with increased dispersion of repolarization is the substrate for reentry and life threatening arrhythmias

- Diagnosis in children may be difficult because the short QT interval may only become apparent at heart rates less than 80 per minute

- Therapies have not been clearly defined, although quinidine may lengthen ventricular refractoriness and reduce vulnerability to VF.

Genetic Electrical Myopathies

- Long QT Syndrome
- Short QT Syndrome
- Brugada Syndrome
- Catecholaminergic Polymorphic Ventricular Tachyarrhythmia (CPVT)

Brugada Syndrome

- First described in 1992
  - 8 patients with right bundle branch block, ST elevation in the right precordial leads and sudden cardiac death.
  - Mean age of sudden death 41 years
  - Incidence not clear, but may be 1 in 2,000.
  - Rare, but can be cause of SCD in children

- 20% - 25% have mutations in SCN5A (Alpha-subunit of Cardiac Na+ channel) – loss of function
  - Other rare gene mutations as well
  - Loss of function can be exacerbated by sodium channel blocking agents (Class I antiarrhythmic medications)
    - medications (procainamide, ajmaline) may be used to unmask the diagnostic ECG findings

Brugada Syndrome

Brugada Syndrome in Pediatrics

- Has been diagnosed in children, generally beyond 5 years of age

- Diagnosis in children is difficult
  - Dynamic ECG findings
  - ECG features which are similar to those characteristic of the Brugada syndrome may occur in healthy young children

- Brugada Syndrome has also been associated with other arrhythmias including sinus node dysfunction, supraventricular and ventricular arrhythmias, and AV node conduction delay
Risk factors for arrhythmic event
- Spontaneous ST-segment elevation in leads V1 through V3 (as opposed to diagnostic ECG findings only after sodium channel blocker challenge)
- History of syncope
- Induction of VT or VF by programmed electrical stimulation has not been a consistent risk factor for SCD.

Fever associated with events

Quinidine can normalize ST and decrease risk for arrhythmias

Remember the classic Brugada ECG:

ECG findings may only show up at a later age (>5 years), so continue to follow if clinical concern

Genetic testing is of limited utility (sensitivity 25-40%)

Fever associated with events in children
Genetic Electrical Myopathies

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Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

- Catecholaminergic VT is a malignant disorder that presents in childhood or adolescence as syncope, polymorphic VT or SCD preceded by exertion or stress

Hypersensitivity to inward calcium currents and abnormal release of calcium ions from the sarcoplasmic reticulum.

- Calcium overload results in delayed cardiac afterdepolarizations, which trigger ventricular arrhythmias.
- Adrenergic stimulation due to emotional stress or physical activity can lead to calcium overload and precipitate tachyarrhythmias

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

- Catecholaminergic VT is a malignant disorder that presents in childhood or adolescence as syncope, polymorphic VT or SCD preceded by exertion or stress.
- Genetically heterogeneous, involving mutations in the cardiac ryanidine and calsequestrin receptors.
  - Ryanidine Receptor (RyR2) - mediates the release of calcium from the sarcoplasmic reticulum that is required for myocardial contraction. Autosomal dominant.
  - Calsequestrin (Casq2) - Major calcium reservoir within the sarcoplasmic reticulum of cardiac myocytes. Autosomal recessive.

Genetically heterogeneous, involving mutations in the cardiac ryanidine and calsequestrin receptors.

George et al. Circ Res 2003;93:531
Yano et al. Mol Cell Biochem 1994;135:61

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

- Frequent ventricular ectopy and ventricular tachycardia with exercise.
- Incidence ~1 in 10,000.
- 30% have family history of sudden death before age 40.
- Genetic testing positive in ~70% (RYR2, Casq2).
- Hoffman et al.: 25 Sudden deaths (age 1-18 years) without initially clear etiology.
  - 14 with disease identified (after testing of patients and families)
    » 7 LQT
    » 3 CPVT
    » 2 HCM
    » 1 ARVD
    » 1 myocarditis.

Hoffman et al. Pediatrics 2007;120; e967-e973
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) 
Bidirectional VT


CPVT – Rx with beta-blockers

- 101 patients, follow-up 7.9 years
- Cardiac events: syncope, aborted cardiac arrest, appropriate ICD discharge, SCD
- 8-year event rate: 32%
  - On beta-blockers: 27%
  - Not on beta-blockers: 58%
- Age at first symptom 12 ± 8 years
- Age at diagnoses 15 ± 10 years
- Independent predictors of events
  - Younger age at diagnoses
  - Not taking beta blockers

CPVT – Other Rx options

- Calcium channel blockers plus beta-blockers
  - 6 patients (5 with CPVT, 1 with HCM)
  - 3 patients with NS-VT during exercise to none
  - Ventricular ectopy during ETT from 78 ± 59 beats to 6 ± 8 beats
  - One patient from 14 ICD shocks in 6 months to none in 7 months of follow-up

- Flecainide – inhibits cardiac Ryanodine receptor channel (RyR2) – reference 29
  - Suppressed VT in 12 of 12 mice (Casq2 deletion)
  - 12-year-old (homozygous Casq2) and 36-year-old (heterozygous RyR2) – suppressed all arrhythmias

Reference:

CPVT and Sympathectomy

- 3 patients with CPVT and sympathectomy
  - All had persistent events despite beta blockers
  - No events after sympathectomy

Reference:
CPVT “Pearls”

- Always consider CPVT when cardiac events with exercise and normal echo and ECG
- Exercise test is key to diagnosis
- Beta-blockers are first line therapy
- Remember sympathectomy

Thank You
Diagnosis - Holter

- Reason to do:
  - Assess for changes in QTc with changes in heart rate
  - Look for ventricular arrhythmias (41% of LQT patients?)

- Problems: Inaccuracy
  - Study comparing Holter to 12-lead showed Holter underestimated QT in V1 and overestimated in V5.

- Generally, there is a need for caution when using Holters to evaluate QT

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Diagnosis – Exercise testing

- Reason to do:
  - Assess for changes in QTc at peak exercise and RECOVERY

- Problems:
  - Difficult to measure QT during artifact and P-waves merge with T-waves

- Best at 3 minutes of recovery

- Subtype differences
  - LQT1: QTc increases with higher heart rates and change to broad based T-wave
  - LQT2: appearance of a notch at higher heart rates
  - LQT3: normal exercise test

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Diagnosis – electrophysiology study

- Reason to do: ???

- EP testing
  - Torsades inducible in 10% of patients and inducibility of ventricular arrhythmias has not correlated with cardiac events
  - Very limited utility

Bandari et al, Electrophysiology testin gin patients with the long QT syndrome. Circulation 1985; 71:63

Diagnosis

- Genetic Testing…. (~75% positive in LQT)
  - Commercially available
  - Helpful when uncertainty regarding diagnosis
  - Helpful for identifying subtype and therefore management
Brugada Syndrome