Anesthesia
Management of the Patient with Long QT Syndrome

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Objectives
• Briefly discuss the historical background of LQTS
• Present a current definition of Long Q-T Syndrome
• Compare the pathophysiology of the two major forms of congenital (c) LQTS
• Describe the clinical manifestations of the two major forms of c-LQTS
• Discuss current diagnosis and treatment options c-Long QT syndrome
• Describe the pathophysiology and management of torsades de pointes
• Discuss the general anesthetic consideration and intraoperative management of the patient with LQTS
• Outline a proposed peri-operative plan of care for the patient with Long QT syndrome.

GOAL

la substantifique moëlle
A concrete plan of approach with the at-risk patient

Disclaimers
• None

Background
LQTS – A Long Road

GOAL

Background
• 1856: Friedrich Meissner in Leipzig town in German reports:
  – Deaf child drops dead after teacher yelled at her
  – When reported parents said two deaf siblings also died suddenly during emotional events
  – NO ECG then
• 1957: Anton Jervell and Fred Lange-Nielsen describe:
  – 4 in 10 children in Norwegian family were deaf & had recurrent syncope
  – 3 died before age of 10
  – Dramatic QT prolongation on ECG was noted
  – Inheritance appeared to be autosomal recessive
Background

- 1963 Cesarino Romano of Italy and
- 1964 Owen Connor Ward of Ireland
- Independently reported similar clinical syndrome:
  - Sudden death during exercise and emotional events
  - Autosomal dominant inheritance
  - No hearing loss

Attempted Definition

Arrhythmogenic disorder
Characterized by:
- Prolongation of the QT interval on ECG
- Pre-disposes to Polymorphic Ventricular tachycardia
  - Syncope
  - Cardiac arrest
  - Death

Long Q-T Syndrome – Two types

Congenital, inherited (primary)
- Due to genetic mutations of cardiac ion channels

Acquired (secondary)
- Adverse response to medications
- Metabolic or physiologic abnormalities

QT Interval Physiology

- Measured from the start of the QRS complex to the completion of the T wave
- Measured in Leads II, V5 and V6
- Derived from 3-5 cardiac cycles (HR)
- Varies with HR
  - Prolongs with bradycardia
  - Shortens with increased HR

Normal is ≤ 420
QTc is prolonged when

- > 450 msec in men
- > 450 msec in women
Congenital LQTS

Should We Care?

- Incidence: 1:1100 – 3000 (Developed World)
- U.S. 1:7000 persons affected
  - causing 2000-3000 sudden deaths in children and young adults yearly
- One of the most common causes of autopsy negative, sudden unexplained death.
- ~60-70% of new cases diagnosed in females than males but with lesser cardiac event
- In females cardiac events have been correlated to menses – unexplained
- >400 LD genetic mutations assoc. with LQTS
- ~30% of phenotypically affected subjects have no mutation identified on genetic analysis
- 70% of those affected are silent carriers

LQTS A Generic term

Phenotypic description of a group of disorders:
- QT interval prolongation - ECG
- Polymorphic ventricular tachycardia (torsades de pointes -TdP)
- Reported gene mutations lead to excess intracellular positive ions.
- Generally referring to Congenital LQTS

<table>
<thead>
<tr>
<th>Sub-type</th>
<th>Frequency</th>
<th>Gene</th>
<th>Mutation Effect</th>
<th>ECG finding</th>
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<tbody>
<tr>
<td>LQTS 1</td>
<td>30-35%</td>
<td>KVLQT1</td>
<td>Variable Qt interval prolongation</td>
<td>Variable Qt interval prolongation</td>
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<tr>
<td>LQTS 2</td>
<td>25-30%</td>
<td>HERG</td>
<td>Excess Na+ influx</td>
<td>Prolonged Na+ influx</td>
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<td>LQTS 3</td>
<td>5-10%</td>
<td>SCN5A</td>
<td>Reduced Na+ influx</td>
<td>Diphasic or peaked, late-onset, T wave</td>
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<tr>
<td>LQTS 4</td>
<td>3%</td>
<td>ANK2B</td>
<td>Build-up of Na+ within cell and Ca2+ outside of cell</td>
<td>Variable Qt interval prolongation</td>
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<tr>
<td>LQTS 5</td>
<td>1%</td>
<td>Kir6.2</td>
<td>Excess Ca2+ influx</td>
<td>Not defined</td>
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<tr>
<td>LQTS 6</td>
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<td>MRP1</td>
<td>Excess Ca2+ influx</td>
<td>Not defined</td>
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<tr>
<td>LQTS 7</td>
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<td>KCNQ2</td>
<td>Excess Ca2+ influx</td>
<td>Mild prolongation of Qt interval</td>
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<tr>
<td>LQTS 8</td>
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<td>KCNE1</td>
<td>Excess Ca2+ influx</td>
<td>Exaggerated Qt interval prolongation</td>
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<tr>
<td>LQTS 9</td>
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<td>CACNA1C</td>
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<tr>
<td>LQTS 10</td>
<td>extremely rare</td>
<td>SCN4B</td>
<td>Prolonged Na+ influx</td>
<td>Not defined</td>
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</tbody>
</table>
Seizure-like episodes
- Recurrent syncope
- Cardiac arrest
- Seizure-like episodes
- Only 60% are symptomatic at time of diagnosis

**Congenital LQTS**

Characterized by:
- Palpitations
- Recurrent syncope
- Cardiac arrest
- Seizure-like episodes
- Only 60% are symptomatic at time of diagnosis

**Congenital LQTS**

Jeruel and Lange-Nielson Syndrome
- Autosomal Recessive
- Associated with Profound Bilateral Sensorineural (cause is CN VIII or centers in brain) hearing loss (Homo V Heterozygous)
- Runs a more malignant course
- Assoc. with SIDS/SCD

**Romano-Ward Syndrome**

- Autosomal dominant with variable penetrance
- More common form of LQTS
- Only has cardiac manifestations
- 50% never show symptoms
- Death is 1st indication in 10-15% of cases

**Genotypes**

- Six genetic variations assoc. with congenital LQTS
- LQT-1 and LQT-5 assoc. with JNLS
- LQT 1-6 assoc. with RWS
- LQT-1 LQT2 and LQT 3 account for over 90% of cases of congenital LQTS

**LQTS Types (percentages of total confirmed cases)**

- LQTS 1: 37%
- LQTS 2: 3%
- LQTS 3: 58%
- LQTS 4, 5, & 6: 2%
Congenital LQTS

Risk is genotype-dependent

- LQT-1 = ↑ ↑ risk with adrenergic stimuli from emotional stress and exercise (?swimming)
  - AKA “catecholamine dependent”
- LQT-2 = ↑ Auditory stimuli but not exercise
- LQT-3 = Bradycardia from sleep and rest
  - AKA “Pause dependent”

Median ages for 1st cardiac event:
- LQT1 = 9
- LQT2 = 12
- LQT3 = 16

Patients with JLNS likely to have their 1st cardiac event at a younger age
- If untreated, mortality is 20% in year after initial event and 50% within ten years
Congenital LQTS

Diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
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<tbody>
<tr>
<td>Electrocardiogram</td>
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<tr>
<td>QTc min ≥ 440 ms</td>
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<tr>
<td>MT interval (s)</td>
<td>1</td>
</tr>
<tr>
<td>Torsade de pointes</td>
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<tr>
<td>T wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0.5</td>
</tr>
<tr>
<td>Epileptic focality</td>
<td>0.5</td>
</tr>
<tr>
<td>Syncope</td>
<td>0</td>
</tr>
<tr>
<td>With stress</td>
<td>2</td>
</tr>
<tr>
<td>Without stress</td>
<td>1</td>
</tr>
<tr>
<td>Congenital deathness</td>
<td>1</td>
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<tr>
<td>Family history</td>
<td>0.5</td>
</tr>
<tr>
<td>Family members with confirmed LQTS</td>
<td>1</td>
</tr>
<tr>
<td>Unexplained sudden death in first-order family members &lt;30 years</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*QTc calculated with the formula of Bazzet (QTs × 60 / sqrt heart rate).

LQTS

Genetico-Molecular Physiology

Channelopathies

Treatment

- Primary goal is to avoid torsades de pointes
- Avoid triggers such as strenuous exercise (swimming and running)
- Check and correct electrolytes in clinical settings
- Consult cardiologist or cardiac electrophysiologist
- Consider genetic counseling for confirmed LQTS
Congenital LQTS

• LQT-1 & LQT-2
  – β-blockade is the gold standard of treatment
  – Propranolol is drug of choice
    • daily dose of 2-3mg/kg = 210mg for 70kg patient
    • Prevents cardiac events in 70% of patients
    • Nadolol, Atenolol and Metoprolol all show equal effectiveness

• LQT-3
  – Na channel blockers Flecanide (75 to 150 mg twice daily orally) and Mexilitine

Congenital LQTS

Pacemakers and ICDs

– Symptomatic patients despite β-blockade
  – Could be used with β-blockers
  – Pacemaker especially beneficial to LQT-3 patients due to pause-bradycardia induced Tdp.

Congenital LQTS

Left cervicothoracic sympathetic ganglionectomy

• Removal of the first 4 or 5 left thoracic ganglia and total left stellate ganglion
  • In patients with frequent ICD triggers while on beta blockade
  • More effective in LQT-1 patients
  • Does not eliminate risk
  • Not superior to ICD

Gene-specific therapy

• Under investigation
• Experimental models have not changed traditional treatment approaches

Acquired LQTS (a-LQTS)

• Caused by external or iatrogenic factors
• Drugs are the most common cause of a-LQTS
• Aprox. 50 FDA approved drugs are culprits
• Principal ion channel resp. for a-LQTS is the I_{Kr} (HERG)
  – Same implicated in LQTS-2
  – Probable physiologic relationship btw LQTS-2 and drug-induced LQT syndrome
Acquired/Secondary LQTS

**Peri-op related drugs implicated**
- Amiodarone
- Procainamide
- Haloperidol
- Droperidol
- Ondansetron
- Granisetron
- Chloral Hydrate

**Other Drugs**
- Nicardipine
- Geodon (Ziprasidone)
- Fosphenytoin
- Salmeterol
- Methadone
- Sotalol
- Macrolide antibiotics (erythromycin)
- Doxepamine
- Epinephrine

Acquired/Secondary LQTS

**Anesthesia related drugs**
- Midazolam has not been shown to prolong QT interval
- Propofol produces an insignificant QT prolongation compared to Thiopental
  - Another study – shortens QT interval
  - Preferred agent for maintenance (TIVA)
- Vecuronium and Cisatracurium show no QT interval prolongation
- Succynlcholine consistently prolonged QT interval

**Reversals:**
- neostigmine-atropine,
- edrophonium-atropine,
- neostigmine-glycopyrrolate
  - All Prolong the QT interval
- Droperidol 0.75mg IV and Zofran 4mg IV produced similar QT prolongation
- Droperidol 0.625mg did not produce a significant prolongation of the QT interval, compared to saline placebo (separate study).
Volatile Agents
• Sevoflurane, Isoflurane and Desflurane at 1 MAC all prolong the QT interval
  Halothane significantly shortens QT interval
  – But Halothane also sensitizes cardiac myocytes to catecholamines
  – Should be avoided in susceptible patients

Anesthesia related drugs
Volatile Agents
Agents have all been administered safely with peri-operative beta blockade, in patients with known LQTS.

Regional Anesthesia
Study in ASA I and II male patients undergoing elective surgery under spinal anesthesia
Showed significant QT prolongation after onset of blockade

Acquired/Secondary LQTS
• Pre-existing cardiac conditions facilitate drug-induced a-LQTS:
  – Ventricular hypertrophy
  – Myocardial ischemia
  – Myocardial fibrosis
• Sub-arachnoid hemorrhage

Other conditions assoc. with LQTS
• Timothy Syndrome
  – Autosomal dominant inheritance with
    • Structural heart defects, QT prolongation, Syndactyly and autism
• Anderson-Tawil Syndrome
  – Autosomal dominant inheritance assoc. with LQTS
  – AKA LQT syndrome 7
  – Assoc with physical abnormalities of the head, face, and limbs
• Brugada Syndrome
  – Inherited defect in Na+ channels, associated with several ECG patterns

Torsades de…?
progressive change in polarity of the QRS complex

- Triggered by:
  - Decreased outward $K^+$ currents
  - Reactivation of calcium channels (key to EAD maintenance)
  - Reactivation of delayed $Na^+$ channels
- All result in early-after depolarization
  - Delayed repolarization
  - Oscillation of membrane potential
- TdP usually Preceded by a pause in most LQTS cases

Torsades de Pointes (TdP)

ECG & Membrane Potential of Ventricular Cell

Phase 3 = rapid repolarization

Early-After Depolarization

EADs that reach threshold could propagate an action potential
Torsades de pointes (TdP)

- Classic short & long Sequence between the R-to-R interval

Torsades de Pointes

- Typical TdP morphology may not be seen in
  - Single lead monitoring
  - Short runs of torsades
- Early events usually short-lived
- Reading could also be affected by
  - Patient movement
  - Faulty lead placement
  - Bovie interference
  - Static electricity

Torsades de Pointes

Treatment

- Can be self-limiting or life-threatening
- May result in sudden cardiac death
- Short-term treatment for both congenital and acquired LQTS similar
  - Beta-1 adrenergic stimulation is contraindicated in catecholamine-dependent congenital phenotype

Torsades de Pointes

Short-term treatment

- Discontinuation of offending agent
  - Predisposing conditions such as bradycardia and electrolyte imbalances should be identified and corrected
- Defibrillation
  - Ventricular fibrillation requires direct current (DC) defibrillation
  - Is the last resort in stable patients because of known TdP recurrences following cardioversion
- Suppression of EADs
  - Magnesium sulfate is first line of treatment
  - Decreases calcium influx, lowering amplitude of EADs
**Torsades de Pointes**

**TREATMENT**

- **Magnesium sulfate**
  - 2-4gm IV initially in 30-60 seconds
  - Repeat 2nd dose in 5-15 minutes
  - Effective even in patients with normal Mg+ levels
  - Or infusion of 3-20mg/min over 7-48 hours
  - Magnesium sulfate decreases calcium influx, decreasing EAD amplitudes
- Some recommend high normal potassium values
- Lidocaine has an initial beneficial effect but TdP recurs in all cases
- Mexiletine may also be used to suppress TdP.
- Isoproterenol can also be used to accelerate heart rate and override electrical pacing (keeping HR >90 bpm)
  - contraindicated in catecholamine-dependent congenital LQTS
  - Used as interim treatment until overriding pacing can be started.

**Temporary transvenous pacing**

- Effective in both forms of LQTS
- It facilitates repolarizing potassium currents
- It prevents long pauses, suppressing EADs and decreasing the QT interval
- Atrial pacing is preferred mode
  - It preserves the atrial contribution to ventricular filling
  - It results in a narrower QRS complex and hence a shorter QT
  - Pacing should be instituted at a rate of 90-110 bpm until the QT interval is normalized.

**General Anesthetistic considerations for patients with LQTS**

**Management**

- Avoid triggers of QT prolongation and TdP
- Provide Peri-op
  - Anxiolysis
  - β-blockade
  - Analgesia
- Maintain
  - Normothermia
  - Normoxia
  - Euglycemia
  - Normocarbia

**Anesthesia Management**

- Avoid hemodynamic extremes
  - Bradycardia
  - Tachycardia
  - Hypotension
  - Hypertension
- Correct serum electrolytes esp:
  - Potassium
  - Magnesium
  - Prophylaxis beneficial even with normal serum concentrations

- Prevent and treat arrhythmia
  - Cont. ECG monitoring in more than 1 lead
  - If ICD/pacemaker, ensure proper functioning
  - Have defibrillator and temporary pacemaker available
  - Consult cardiology as needed
The Dogs Bark….

…..and the Caravan Goes by!