Long QT syndrome

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KACC
LQTS

• Genetically heterogeneous group of inherited disorder
• ECG remain the corner stone for diagnosis
• Clinical syndrome with increase risk of potential life threatening arrhythmia
Background

• Classically
  – AD – (Romano –Ward)
    • 1:2000 – 1:5000
    • May presented with isolated cardiac phenotype
  – AR – JLNS
    • 1:100,0000 – 1:4000,000
    • May present bilateral sensorineural deafness in addition to malignant cardiac arrhythmia

• LQTS subjected to phenomena of incomplete penetrance and variable expressivity

• Homozygous, compound heterozygous
  – Malignant LQTS1 similar to those JLNS without any discernible deafness (so called AR LQTS1)
Background

- Genetically and phenotypically heterogeneous group of disorders which may include multisystem disorder

- Recently
  - Major genes
    - LQTS1, LQTS2, LQTS3 (75 – 90%)

  - Minor gene
Currently 15 genes have been identified.
Clinical presentation

A. Normal

LQT1

LQT2

LQT3

B. TdP

C. 1. Syncope
   2. Seizures
   3. Sudden Death
<table>
<thead>
<tr>
<th>Type</th>
<th>Current</th>
<th>Functional Effect</th>
<th>Frequency Among LQTS</th>
<th>ECG\textsuperscript{12,13}</th>
<th>Triggers Lethal Cardiac Event\textsuperscript{10}</th>
<th>Penetrance*</th>
</tr>
</thead>
</table>
| LQTS1  | K       | \(\downarrow\)    | 30\%-35\%           | ![ECG](image1)             | Exercise (68\%)  
Emotional Stress (14\%)  
Sleep, Repose (9\%)  
Others (19\%)   | 62\%      |
| LQTS2  | K       | \(\downarrow\)    | 25\%-30\%           | ![ECG](image2)             | Exercise (29\%)  
Emotional Stress (49\%)  
Sleep, Repose (22\%) | 75\%      |
| LQTS3  | Na      | \(\uparrow\)      | 5\%-10\%            | ![ECG](image3)             | Exercise (4\%)  
Emotional Stress (12\%)  
Sleep, Repose (64\%)  
Others (20\%) | 90\%      |
Malignant subtypes

• JLNS (90% of pt have earlier cardiac event)
  – homozygous mutations involve $KCNE1$ instead of $KCNQ1$ are at lower risk.

• Timothy syndrome
  – marked QT prolongation
  – syndactyly
  – often presenting with 2:1 functional atrioventricular block
  – macroscopic T-wave alternans.
  – Congenital heart diseases,
  – intermittent hypoglycemia,
  – cognitive abnormalities,
  – and autism
Diagnosis

• Clinical syndrome
• QTc interval according to guidelines

• (Bazett’s formula) ≥450 ms for HR <75 beats/min and ≥500 ms for HR ≥75 beats/min
  • diagnose 94% genotype-positive LQTS cases
<table>
<thead>
<tr>
<th>Electrocardiographic findings*</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>A QTc,† ms</td>
<td></td>
</tr>
<tr>
<td>≥480</td>
<td>3</td>
</tr>
<tr>
<td>460–479</td>
<td>2</td>
</tr>
<tr>
<td>450–459 (men)</td>
<td>1</td>
</tr>
<tr>
<td>B QTc† 4th minute of recovery from exercise stress test ≥480 ms</td>
<td>1</td>
</tr>
<tr>
<td>C Torsades-de-Pointes‡</td>
<td>2</td>
</tr>
<tr>
<td>D T-wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>E Notched T wave in 3 leads</td>
<td>1</td>
</tr>
<tr>
<td>F Low heart rate for age§</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Clinical history

| A Syncope‡                     |        |
| With stress                   | 2      |
| Without stress                | 1      |

Family history

| A Family members with definite LQTSII | 1      |
| B Unexplained sudden cardiac death younger than age 30 among immediate family members | 0.5   |
Diagnosis

- Atypical case
- Latent case
  - 36% of LQT1
  - 19% of LQT2
  - 10% of LQT3
QT interval: what is normal?

knew how to measure it properly

- < 40% of physicians other than cardiologists
- < 50% of cardiologists
- > 80% of specialists in arrhythmia

Diagnostic modalities

- Holter
- Exercise stress test
- Standing
- Epinephrine provocative test
- Torsade de pointe
  - Self-limited
  - Cardiac arrest
- T wave morphology
- Sinus pause (unrelated to sinus arrhythmia)
  - Warning sign
  - LQT3
Exercise stress test

- 69 relatives of LQT1 and LQT2 probands who showed borderline to normal QTc at rest
- 4-min recovery QTc
  - ≥445ms discriminated LQTS gene carriers from non-carriers
  - 4-min recovery ≥480 ms (100% specificity)
exercise testing of 243 patients
- (QTc ≥460ms) distinguished LQTS, particularly LQT1
- (QTc 3-min recovery – baseline supine QTc)= ≥30 ms
  • Sensitivity 83%
  • specificity 93%
Epinephrine QT Stress Test

10 min 10 min 5 min 5 min 5 min 10 min
Baseline 0.025 0.05 0.1 0.2 Recovery

Epinephrine (mcg/kg/min)
Genotype vs Phenotype

- None of the cases with a positive genotype had a QTc <410 ms
- None with a negative genotype had a QTc > 470 ms.
- QTc > 440 ms suffices to detect patients with LQTS-associated mutations
- QTc > 470 ms is useful to identify patients at risk of developing symptoms
- QTc > 500 ms is found in symptomatic patients undergoing treatment.


Monnig G, Eur Heart J. 2006
Not All Beta-Blockers Are Equal in the Management of Long QT Syndrome Types 1 and 2

Higher Recurrence of Events Under Metoprolol

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