Rett Syndrome and Long QT

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Topics to cover

What is the QT interval?

What is the QTc (corrected QT interval)?

Why does it get prolonged?

Why do we care?

What is the relationship to Rett Syndrome?

What should be done?
What is the QT interval?
The ECG represents the electrical signal as it passes through the heart muscle.

- It is a “global” representation.
- Minimal fine detail.

Channels in the heart muscle cell allow electric current to pass through and this makes the ECG pattern.
Heart channels are like pipes
Defective manufacturing lets too much or too little through
The manufacturing process is in the genes
The genetic test can diagnose which pipe is defective (fine detail)

Starting to tell us what treatment may be best
Also, how much risk there is
Measurement reminder

- P wave
- QRS complex
- ST segment
- T wave
- U wave

**Intervals:**
- PR interval
- QRS interval
- QT interval
What is the QTc (corrected QT) and why do we need it?

QT gets shorter as heart rate increases – therefore no single “number” which defines normal

Bazett formula: \[ QTc = \frac{QT}{(HR/60)^{1/2}} \]
Normal QT/QTc intervals

Not ≤ 440 msec (in old books etc)

**Rijnbeck et al (now most commonly used)**

(98th %ile)

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<th>0-1m</th>
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<th>3-6m</th>
<th>6-12m</th>
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**Mason et al (large population based study)**

<table>
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<th>Mean (SD)</th>
<th>Overall</th>
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<td>409 (21)</td>
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<tr>
<td>F 10-19</td>
<td>457</td>
<td>402 (23)</td>
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What about measuring the QTc and how do we get measurements?

Automatically from the ECG printout relies on an algorithm to detect end point of T wave

Hand measuring there are reliable methods to measure

Studies show that most physicians cannot measure the intervals correctly, or interpret the data this is a specialized area of cardiology

Even physicians who are “expert” will get slightly different Numbers each time they measure the ECG
QTc 487

448 msec by hand

QTc above normal limits; HR > 100/m
Why does the QT get prolonged?

Congenital
  Mutations in genes that control the manufacture of genes that make the channels
direct effects or secondary effects
(3 main types: 1,2,3)

Acquired
  Function of channels changed by extraneous forces
  medication
  heart failure
  electrolyte problems (K, Ca)
  abnormal muscle
Sodium (Na)
Calcium (Ca)
Potassium (K) 2 types

PR interval
QRS interval
QT interval
Main problems are Na channel and K channel

Na channel

• should close quickly
  • does not in LQTS3
  • current last longer than it should
  • activation lasts longer

K channel

• should open fully
  • does not in LQTS1, LQTS2
  • delays current flow for recovery
  • recovery takes longer

Manufacturing changes in congenital form
Acquired form – think of something building up to change the function
Medications that lengthen the QT/QTc

Antibiotics
- azithromycin
- ciprofloxacin
- erythromycin
- trimeth/sulf

Seizure medication
- felbamate

Psychological medication
- fluoxetine
- imipramine
- trazadone

Antiviral
- amantadine

GI
- domperidone

Antihistamines
- diphenhyramine
- hydroxyzine
Why do we care about a prolonged QT/QTc?

LQTS and Torsade de Pointes

Potentially lethal arrhythmia

If brief it causes sudden fainting with quick recovery

May be seizure like activity – brief if recovery

Sudden death if prolonged

Prolonged seizure with recovery is not a LQT arrhythmia
Event free survival by QTc quartile - 1st < 446 msec
- 2nd < 468 msec
Congenital LONG QT syndrome

Found in 1 person per 2000 to 2500 people in the community

One of the leading causes of sudden death in otherwise healthy young people who die suddenly and unexpectedly when nothing found to explain death at an autopsy

Most forms are inherited (from parents to children)

Traditionally diagnosed on electrocardiogram

The electrocardiogram may be inconclusive in 20% to 40% of cases

In these, the diagnosis may only be confirmed or excluded by genetic testing

In those people with a known causative gene defect, the genetic test will be conclusive in other family members
Congenital LONG QT syndrome

Individuals with LQTS have an increased risk of sudden death compared with general population (10 to 40 times) depending on multiple factors (including specifics from genetic test)

Relatively simple measures can substantially reduce the risk in most medicines called beta blockers (block adrenalin’s effect) avoiding certain prescription or over-the-counter medicines avoiding dehydration modification of activity in many

People with the highest risk profile often require a multidisciplinary approach

Long term outlook is excellent with modern management

Probability of a female having these 2 independent conditions (RTT and cLQTS) is 1 in 25-30 million live female births)
What is the relationship between LQTS and Rett Syndrome?

Sudden unexplained death in RS
   26% in Registry

Clinical associations

Sekul et al 1994
   34 patients with Rett Syndrome
   QTc ≥ 0.45
   14/34 (41%)

Ellaway et al 1999
   34 girls with RS
   QTc > 0.45
   9/34 (26%)

McCauley et al 2011
   379 females
   QTc > 0.45
   18.5 % long QT
What is the relationship between LQTS and Rett Syndrome?

Experimental data

McCauley et al 2011
Mouse model
Put MeCP2 gene in males and females
QT was longer
Heart irregularities induced (death)
Na channel function abnormal
Prolonged current (like LQTS3)
even when mutation only in brain
Corrected by phenytoin (dilantin)

Hara et al 2015
Mouse model
MeCP2 produces structural changes in heart cells

De Felice et al 2012
Subtle changes in heart contraction and relaxation in patients
What is the relationship between LQTS and Rett Syndrome?

Is the association true?
Too early to say

MeCP2

Channel abnormality

Structural changes in cell

Long term follow-up studies have not (as yet) confirmed a causal relationship between QTc and increased risk of death
What is the relationship between LQTS and Rett Syndrome?

Two things being associated does not establish a causal link

There are very specific criteria to “establish” a causal link

The way this is studied is different

In this case:

- Do ECGs on all people diagnosed with RTT (very early)
- Follow them for a long time
- Need large numbers to balance out many factors
- See if QTc longer in those who died compared with those who did not
- Make sure all “confounders” are balanced
  - medicine, seizures

Not established so far
OK, now what?

How should this be managed?

ECGs at diagnosis and during follow-up

If QTc prolongation (age, gender, heart rate) is suspected from a single ECG, repeated 2-3 times over one to two months

If able, an exercise test to examine the dynamics of the QT interval (possibly a standing test, rarely drug challenge test – eg adrenaline)

If “confirmed” management depends on length of QTc

(in individuals without heart related symptoms, the international guidelines state LQTS should not be diagnosed unless QTc > .48 (and usually .5))

Therefore marginal lengthening is usually NOT considered a sign of increased risk
OK, now what?

How should this be managed?

- Differentiate fainting from seizures

- Prudent to avoid medication that further prolongs the QT interval (if medically possible)

- Follow-up and keep an open mind

- I would not recommend β-blockers except under exceptional circumstances (open to discussion)

- Further research needed
Questions?