Long QT syndrome (LQTS)

- A disorder of myocardial repolarization characterized by a prolonged QT interval on ECG.
- ↑ risk of a characteristic life-threatening cardiac arrhythmia, known as torsade de pointes (TdP) VT.
- Drug induced usually with bradycardia
- Short-long cycles 2ⁿ VPBs
- Present with:
  - Palpitations
  - Syncope
  - Seizures
  - Sudden cardiac death (SCD)
- Congenital – 2 phenotypes
  - Romano – Ward: more common, purely cardiac
    - Autosomal dominant
  - Jervell + Lange-Nielsen: sensorineural deafness
    - Autosomal recessive
- At least 7 genes described LQTS 1 - 7
- Affect Na and K channels
- Acquired LQTS may be a ‘forme fruste’

Acquired LQTS

- Commonest causes
  - Medications
  - Electrolyte disorders
- Others
  - Structural heart disease
  - Stroke + brain injury
  - HIV
  - Eating disorders
Long QT of Hypocalcemia

**Polymorphic ventricular tachycardia in ischemia** Rhythm strip reveals several episodes of nonsustained ventricular tachycardia (VT) occurring during an acute ischemic event. The QRS complexes are variable in morphology and RR intervals; thus, the VT is polymorphic. The QT interval is normal. This form of VT should be distinguished from torsade de pointes in which polymorphic VT is associated with QT interval prolongation.
Drug Induced LQTS

- First recognized in 1920s – quinidine syncope
- Monitoring identified typical sequences in TdP in 1960s
- In the past decade, the **single most common cause** of the withdrawal or restriction of the use of drugs that have already been marketed has been the prolongation of the QT interval associated with polymorphic ventricular tachycardia, or torsade de pointes.
- Nine structurally unrelated drugs removed or severely restricted due to QT ↑ + TdP.

Risk Factors for TdP

- **Drug regimen:**
  - Not usually an idiosyncratic event
  - ↑ drug dose or concentration (except quinidine)
  - Rapid IV infusion
  - Concurrent drugs
    - That ↑ QT
    - ↓ metabolism: cytochrome P450 inhibition
      - Erythromycin does both!
- **Metabolic factors**
  - Electrolytes: ↓K, ↓Mg, (↓Ca)
  - Impaired hepatic or renal function
- **Other**
  - Heart disease: CHF, LVH
  - Recent conversion from atrial fibrillation
  - ♀ gender
- **ECG abnormalities**
  - Baseline QT ↑ or T wave lability
  - The development of marked QT ↑, T wave lability, or T wave morphologic changes during therapy
  - Bradycardia → ↓ extracellular K, → ↑ drug-induced inhibition of IKr
  - Congenital long QT syndrome or "silent" mutations in LQTS genes
- **Drugs include:**
  - terfenadine, astemizole, grepafloxicin, terodiline, droperidol, lidoflazine, sertindole, levomethadyl, and cisapride.
Methadone-induced QTS

Acquired LQTS
- Drugs block outward IKr current
- IKr responsible for phase 3 repolarization,
  - ↑ phase 3 repolarization → QT↑
  - QT ↑ → ↑ spatial dispersion of repolarization

Why the IKr Channel in LQTS?
- ↑ inner cavity size in IKr channel
- → trapping of large molecules
- Aromatic residues bind large aromatic drugs
- APD prolongation with IKr blockade is non-uniform → QT dispersion throughout the myocardium
- “reverse frequency dependent”

So What?
- Early after-depolarizations (EAD) can induce triggered beats.
- EADs can infringe on the underlying substrate of inhomogeneous repolarization (M cells) to initiate re-entrant excitation → TdP

Drugs + Acquired LQTS
- Among 761 cases of drug-induced TdP reported to the World Health Organization Drug Monitoring Centre between 1983 and 1999, the most common drugs were sotalol and cisapride (17 and 13 percent)
- Antiarrhythmic drugs: class I + III; responsible in ¾ cases
Nonsedating antihistamines
- Erythromycin: 2 fold ↑ in SCD
- Metabolized by CYP3A4 system
- Patients taking diltiazem, verapamil, troleandomycin, azole antifungals → 5x risk of SCD if taking erythromycin.

Macrolide antibiotics
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Antipsychotics + antidepressants
- Drugs recently d/c due to ↑ QT:
  - Cisapride
    - In Children:
      - N = 35, mean age 5.2 years, rx for reflux.
      - ↑ QT in 31%, TDP in 5.7%
  - Terfenadine
    - Very potent IKr blocker
    - Nearly completely biotransformed by the CYP3A before entering the systemic circulation.
    - Its major metabolite, fexofenadine, is noncardioactive, marketed as Allegra.
    - Problems occur with:
      - Inhibition of CYP3A - erythromycin or ketoconazole
      - CYP3A overwhelmed ie. an overdose
      - Reduced activity by disease (such as cirrhosis)
      - Terfenadine levels ↑ markedly, → ↑↑ QT
  - Astemizole

VT in Acquired LQTS
- Usually bradycardia or frequent pauses precede VT, ie ‘pause-dependent’
- VT commonly ‘short – long’ RR intervals
- VPB → pause → further ↑ QT
- Next VPB in longer QT → VT
- LQTS drugs → ‘reverse use dependence’
  - ie ↓ rate → >> ↑ QT

Extremely prolonged QT & bizarre T wave
What about quinidine syncope?

- TdP occurs at sub-therapeutic levels: 1st dose
- Low levels: potent IKr blocker
- Higher levels: Na channel blocker dominates which may protect against TdP

‘Reduced repolarization reserve’

- A spectrum of ‘normal’ repolarization, not apparent in the basal state.
- Exposure to QT↑ drugs, ∆metabolic state → marked QT↑ in susceptible individuals.
- TdP risk also varies for similar degrees of QT prolongation.
- QTc > 500 ms, should prompt consideration of medication change.
What’s different about females?

♀ have:
- longer QT
- greater response to drugs blocking IKr
- estrogen potentiates bradycardia induced ↑QT
- androgens ↓QT and → less drug responsive

When prescribing drugs affecting QT
- Caution when 1≥ risk factors present
- Consider alternative agents
- Baseline and interval ECG for QTc
- Instruct pts to report
  - Palpitation, syncope, near syncope
  - Report changes that $\rightarrow \downarrow K^+$ (ie. GI Δs, diuretics)

**QT measurement**
- Lead II: beginning of QRS to end of T wave
- Corrected to rate with Bazett’s formula
  - QTc = QT interval $\div \sqrt{RR}$ interval (in sec)
  - Normal QTc:
    - $\text{♂} \leq 440$ ms
    - $\text{♀} \leq 460$ ms

**Prolonged QT interval** The corrected QT interval (QTc) is calculated by dividing the QT interval (0.60 seconds) by the square root of the RR interval (0.84 seconds). In this case, the QTc is 0.65 seconds.

**Rx for Drug-induced TdP**
- Unstable pt: nonsynchronized DC cardioversion
- Stable or to prevent recurrence
  - MgSO$_4$: 2 g / 1-2 min with repeat or infusion, correct K+
  - Isoproterenol: 2g/500 to $\uparrow$ HR $\sim 100$ bpm
  - Overdrive pacing: atrial or ventricular, $\downarrow$ QT+dispersion
  - Screen family members for congenital LQTS
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The Bad News

- Torsade de pointes (TdP) ventricular tachycardia is often unheard and fatal.
- TdP often occurs without apparent structural heart disease.
- TdP often occurs in young healthy patients.
- TdP can occur with commonly Rx drugs.

The Good News

- TdP can be prevented with good Rx habits and heightened level of awareness.
- Most TdP occurs in presence of risk factors.
- Close monitoring can prevent most cases.

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Hemodynamic & ECG monitoring
- Review drug history thoroughly
- Discontinue all QT-prolonging drugs
- Suppress EADs
  - MgSO4, i.v. bolus, 2 gm/1-2 min, twice if necessary, then i.v. infusion 3-10 mg/min
  - Shorten QTc
    - Lidocaine, i.v. bolus, 1-2 mg/kg, twice if necessary, then i.v. infusion 2-4 mg/min
    - KCl, i.v. infusion, 1.5 gm/hr, to serum K > 4 meq/L, better to ≥ 4.5 meq/L
    - Increase ventricular rate (VR)
      - Isoproterenol, i.v. infusion, 1-4 ug/min to keep VR to 100-120/min
        (Must R/O Congenital LQTS)
      - Cardiac pacing to 120-140/min

Check possibility of Congenital LQTS
- Previous ECGs, serial ECGs
- Personal history or family history of syncope, TDP, or cardiac arrest
- Molecular genetic testing

Congenital LQTS
- Life-long avoidance of QT-prolonging drugs or conditions
- Beta-blockers (maximal dose)
  + Cardiac pacing, if bradycardia or AVB
  + Left cardiac sympathetic denervation if beta blockers + pacing fail
  + Implantable cardioverter defibrillator
    - if all of the above fail
    - or if patient has symptoms before treatment
    - or if the first symptom is cardiac arrest
  + Gene-based specific therapy (see text)
  + "Life style modification" (see text)

Acquired LQTS
- Avoid QT-prolonging drugs in the future
  - If QT-prolonging drugs must be used
    + Hospitalize patients for close monitor of QTc for 72 hrs
    + Avoid 2nd QT-prolonging agents or conditions
    + Avoid known inhibitors of CYP for the metabolism of the drug
    + Avoid hypokalemia, hypomagnesemia, and hypocalcemia
    + Avoid bradycardia