Getting to the Heart of Genetics Arrhythmias and Cardiomyopathies

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Getting to the Heart of Genetics
Arrhythmias and Cardiomyopathies

Presenter Disclosure:

Susan Conacher has no potential for conflict of interest with this presentation.
Inherited Heart Rhythm Disorders
• Long QT (Short QT)
• CPVT - Catecholamnergic Polymorphic Ventricular Tachycardia
• Brugada Syndrome

Cardiomyopathies
• ARVC - Arrhythmogenic right ventricular cardiomyopathy
• HCM - Hypertrophic Cardiomyopathy
• DCM - Dilated Cardiomyopathy
• LVNC - Left ventricular Non-compaction

Familial Aneurysms
• Familial TAAD (Familial thoracic aortic aneurysm and dissection)
• Marfan Syndrome
• Loeys-Dietz Syndrome
• Ehlers-Danlos Syndrome (vascular type)
Illustration showing prolonged QT interval on an electrocardiogram (ECG)
Long QT Syndrome

• optimal cut-off value to distinguish affected
  (≥420 for men and ≥440 QTc for women)
• >499ms significant risk of events
• History of syncope is most powerful indicator of SCD risk
  Syncope <18 years 18 fold increase in SCD
  Syncope >18 years 5 fold increase in SCD

STRESS TEST – most useful test for diagnosing LQT
LQT treatment /counselling

- Beta blockers
- ICD (only if cardiac arrest or beta blocker resistant)
- Exercise avoidance (Competitive training)
- Avoidance of LQT prolonging drugs
- Family screening
Guest View: Combined List of All QT Drugs and List of Drugs to Avoid in Patients with Congenital Long QT

To sort the List and to have access to the subsets of these lists that are based on risk categories (Risk of TdP, Possible Risk of TdP and Conditional Risk of TdP), please log in or register to become a member.

For 2 page printable PDF of Combined QT drugs list, click [here](https://www.crediblemeds.org/). For the Spanish version click [here](https://www.crediblemeds.org/es/).
For 2 page printable PDF of Drugs to Avoid in Patients with Congenital Long QT, click [here](https://www.crediblemeds.org/). For Spanish version click [here](https://www.crediblemeds.org/es/).

Please select the list: **Drugs to be avoided by congenital Long QT**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Names</th>
<th>Drug Class</th>
<th>Therapeutic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albuterol (salbutamol)</td>
<td>Proventil®, Ventolin®, Ventolin-HFA®, Accuneb®, Combitvent®, Vospire-ER®, ProAir HFA®, Duoneb®</td>
<td>Bronchodilator</td>
<td>Asthma</td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>Uroxtat®</td>
<td>Alpha-blocker</td>
<td>Benign prostatic hyperplasia</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Symmetrel®, Symadine®</td>
<td>Anti-viral</td>
<td>Anti-infective/ Parkinson's Disease</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Cordarone®, Pacerone®, Nextorone®</td>
<td>Anti-arrhythmic</td>
<td>Abnormal heart rhythm</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>Solian®, Supitac®, Soltus®, Ambrex®, Amazed®</td>
<td>Anti-psychotic, atypical</td>
<td>Psychosis</td>
</tr>
<tr>
<td>AmintriMine</td>
<td>Flxal® (Discontinued 1/13)</td>
<td>Anti-depressant</td>
<td>Tricyclic depression</td>
</tr>
</tbody>
</table>
Brugada Approach London

Genetics or Urgent Clinic
Genetic Testing
Consider ICD

ECG Guide
Type 1
Type 2
Type 3

Brugada ECG*

Type 1
Type 2 or 3

Procainamide Infusion
High Leads and SAECG

Genetics Clinic

Type 2 or 3
Type 1

Reassurance
Risk Discussion
± EP Study§
± Genetic Testing¶

* ECG should include high lead placement, and baseline signal averaged ECG
§ Discretionary EP testing, generally discouraged
¶ CCS Guidelines recommend genetic testing when there is a positive family history or phenotypically affected first degree relative
Standard type 1 Brugada pattern advice

1. Treat fever

2. Avoid specific drugs (www.brugadadrugs.org)

3. Report syncope, seizures, sleep disturbance

4. Family screening
Drugs to be avoided by Brugada syndrome patients

The following drugs have been associated with arrhythmias and the typical (type-1) Brugada syndrome ECG. Therefore the BrugadaDrugs.org Advisory Board strongly advises to avoid these drugs in Brugada syndrome patients or to use these drugs only after extensive consideration and/or in controlled conditions.

Notes about the lists:

- On this list we summarized those drugs for which there is literature available for an association between the drug and arrhythmias in Brugada syndrome.
- Drugs are listed with up to 3 common brand names. There may be over 100 different brand names for different drugs, an effort to list those we know of you can find here. It is also important to look at the active drugs in medicines that contain a combination of drugs.
- Lists contain links to DrugBank or PubChem (click on the drug name) and also (several)
Catecholamenergic Polymorphic Ventricular Tachycardia (CPVT)

Ventricular tachycardia caused by increased heart rate in response to physical activity or emotional stress.

Ventricular tachycardia can degenerate into ventricular fibrillation causing sudden cardiac death.

Onset is often early in life between 7-12 years but also has presented in the 4th decade of life.

Highly penetrant – up to 80% experience at least one syncopal episode and 30% cardiac arrest.
Inherited Heart Rhythm Clinic

Reasons for referrals
• Abnormal ECG
• Unexplained cardiac arrest
• Family history inherited arrhythmia condition
• SCD in family
“Each death of a child under five is reviewed by the Death Under Five Review Committee of the Office of the Chief Coroner. After their this review, they suggested that your child’s **first degree relatives (parents, brothers and sisters)** be assessed by a **cardiologist** who specializes in inherited heart rhythms. This suggestion was made because the cause of your child’s death was uncertain and could have been due to a heritable cardiac conduction disorder that could cause irregularities of the heart rhythm which could lead to serious consequences.”
Post mortem recommendations

Recommend saving appropriate sample 5-10mls EDTA for SUDS and SIDS with a negative autopsy.

Genetic studies in SIDS cases suggest that up to 10-15% of SIDS cases may stem from an underlying inherited arrhythmia (mainly LQT).

Post-mortem genetic testing (molecular autopsy) of the various cardiac arrhythmia genes has revealed a cause of death in up to 35% of these SUD cases.”
Inherited Heart Rhythm Clinic

• Family oriented
• Key element is a **thorough history**
  not just syncope and sudden death
  – Miscarriages, stillbirths, SIDS, drowning and accidents,
  – triggers
  – Syncope (most commonly vasovagal careful history can help determine if it was a cardiac syncope)
  – Up to 25% of people will have a warning event prior to cardiac arrest
• Medication history (prescription, non-prescription and illicit drug use)
• Targeted investigations determined by previous investigations and clinical history.
  – Monitoring, imaging, provocation, **genetic testing**
Family Screening

The majority of cardiac conditions we currently genetically test for are inherited as autosomal dominant conditions.
Cardiomyopathy Panel – 76 genes

ABCC9, ACTC (ACTC1), ACTN2, ANKRD1, BAG3, BRAF, CAV3, CRYAB, CSRP3, DES, DMD, DSC2, DSG2, DSP, DTNA, EMD, FKTN, GATAD1, GLA, HRAS, ILK, JPH2, JUP, KRAS, LAMA4, LAMP2, LDB3 (ZASP), LMNA, MAP2K1, MAP2K2, MTND1, MTND5, MTND6, MTTD, MTTG, MTTH, MTTI, MTTK, MTTL1, MTTL2, MTTM, MTTQ, MTTS1, MTTS2, MYBPC3, MYH7, MYL2, MYL3, MYLK2, MYOZ2, MYPN, NEBL, NEXN, NRAS, PDLIM3, PKP2, PLN, PRKAG2, PTPN11, RAF1, RBM20, RYR2, SCN5A, SGCD, SOS1, TAZ, TCAP, TMEM43, TMPO, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, VCL
Arrhythmia Panel – 32 genes

AKAP9, ANK2, CACNA1C, CACNB2, CASQ2, CAV3, DSC2, DSG2, DSP, GPD1L, HCN4, JUP, KCNE1, KCNE2, KCNE3, KCNH2 (HERG), KCNJ2, KCNJ5, KCNJ8, KCNQ1, NKX2.5, PKP2, RANGRF (MOG1), RYR2, SCN1B, SCN3B, SCN4B, SCN5A, SNTA1, TMEM43
## Genetic Testing

### LQT Genes

<table>
<thead>
<tr>
<th></th>
<th>LQT1</th>
<th>LQT2</th>
<th>LQT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNQ1</td>
<td>58%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KCNH2</td>
<td>35%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCN5A</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Beta blockers**: ++++ + +
- **Triggers, symptoms**: Exercise, swimming
- **Event less than <40 years**: 25% 50% ?
- **LQT Genes**: AKAP9, ANK2, CACNA1C, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, SCN4B, SCN5A, SNTA1
## Genetic Testing

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yield from genetic testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT</td>
<td>75%</td>
</tr>
<tr>
<td>CPVT</td>
<td>50-55%</td>
</tr>
<tr>
<td>BrS</td>
<td>20%</td>
</tr>
<tr>
<td>ARVC</td>
<td>30-40%</td>
</tr>
<tr>
<td>HCM</td>
<td>50-55%</td>
</tr>
<tr>
<td>DCM</td>
<td>10%</td>
</tr>
</tbody>
</table>
Evaluating Relatives

• Relatives often asymptomatic may not understand decreased penetrance and variable expressivity
• Pressure to test family members for informativeness
• When to test children
• Confidentiality/privacy issues
Referrals for cardiac evaluation and genetic testing

- Long QT (short QT)
- CPVT
- Brugada
- ARVC (presentation and management mainly “electrical”)

- HCM, DCM, LVNC

- Familial TAAD
- Marfan Syndrome
- Loeys-Dietz Syndrome
- Ehlers-Danlos Syndrome (vascular type)

Inherited Heart Rhythm Clinic
Cardiomyopathy clinic
Medical Genetics
Questions?