Syncope in Inherited Arrhythmias

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What is the main difference between syncope and SCD in Hereditary Arrhythmogenic Genetic Disorders?

- **Syncope** may occur due to self-terminating VF episodes
Hereditary Arrhythmogenic Syndromes

- LQTS
- Brugada syndrome
- Catecholaminergic polymorphic ventricular tachycardia
- Short QT syndrome
- Early Repolarization?
- Idiopathic VF?

Structurally Normal Heart

??
Predictors of Cardiac Syncope

• During effort or while supine
• Palpitations followed by syncope
• History of structural heart disease
• Family history of unexplained sudden death or an inherited condition
• Abnormal ECG
A. Medical History
A. Medical History

1. Family history

2. Circumstances of syncope

3. Symptoms
1. Family History

• Hereditary Arrhythmias

• Sudden death in young relative (<40)
  • Patients admitted with syncope to A&E
    • Those with FH of SCD, more frequently had LQTS
      • Colman et al. 2008 Europace

• In some cases this may be the only clue
  • "Normal" ECG / ECG with concealed changes

• Patients **MUST** undergo exhaustive testing
Questions to ask when considering a diagnosis of channelopathy.

Does the patient have a history of syncope?
Is there a history of syncope in the patient's family?
Are there any relatives in the patient's family who have had a sudden unexplained death?

**Is there a history of drowning in the patient's family?**
**Have there been any suspicious motor vehicle accidents?**
2. Circumstances preceding the Syncopal Event

• Specific situations/triggers for the different syndromes
  • Diagnosis / directing investigation

• Exercise
  • LQTS
    • 62% of LQT1
    • 13% of LQT3
    • LQT2 intermediary results
      • Schwartz 2001 Circulation
  • CPVT

• During exercise (++)
  • Immediately on cessation (+ VVS)
Triggers for Cardiac Events

- LQT1 (n=358)
  - Exercise: 68%
  - Emotion: 28%
  - Rest, sleep: 4%

- LQT2 (n=177)
  - Exercise: 15%
  - Emotion: 51%
  - Rest, sleep: 34%

- LQT3 (n=43)
  - Exercise: 19%
  - Emotion: 28%
  - Rest, sleep: 53%

www.escardio.org
2. Circumstances preceding the Syncopal Event

• Swimming
  • LQT1

• Sudden Loud Noise
  • LQT2
    • Moss 1999 Am J Cardiol
    • Wilde 1999 JACC

• Sleeping or rest
  • 39% of LQT3
    • Schwartz 2001 Circulation

• Stress and Supine
  • LQT1 and 2
    • Colman 2008 Europace
  • CPVT (+Stress)
    • Adler 2015 Cardiol Clin
3. Symptoms

• Before
  • No or little prodrome

• Cyanosis

• Following
  • Delay in regaining consciousness even after assuming supine position
  • Associated trauma due to sudden fall
3. Symptoms

• Suggestive arrhythmic syncope
  • Brugada patients with syncope followed during 65 months
    • 5% spontaneous VF during 65 months in Brugada patients
    • 0% in those with non-arrhythmic or doubtful
      • Sacher 2012 Heart Rhythm

• LQTS vs VVS
  • Palpitations prior to syncopal event are more frequent in LQTS
  • LQTS patients – 18% had symptoms similar to VVS (coughing, micturition, defecation)
    • Colman 2008 Europace

• Can't always rely on symptoms to differentiate!
3. Symptoms

- Spontaneous VF in BrS patients presenting with arrhythmic syndrome
  - Intermediate risk (15%) at 9 years FUP
    - < post-aborted SCD (53%) > asymptomatic (3%)

- Patients with prodrome of "blurred vision"
  - Very low risk
    - Take et al. 2012 Heart Rhythm

- However, vagal stimulation may be pro-arrhythmogenic
  - Miyazaki et al. 1996 JACC

- Atrial fibrillation at a young age
  - BrS
  - SQTS

- **Agonal respiration** and difficulty in arousal at night may be due to self-terminating VF
3. Symptoms

• Distinction between "Malignant Arrhythmogenic Syncope" vs. "Seizures"
  • Difficult task
  • True tonic-clonic movements – only epilepsy
  • MAS – tonic movements occur commonly
    • However, these are not witnessed by the physician

• Post-ictal phase – epilepsy (minutes to hours) - drowsiness and confusion

• If Pt fully alert immediately after syncope with tonic-clonic movements
  • consider arrhythmogenic syncope until proven otherwise
Recent syncope vs. Remote syncope

• Recent (+ concerning) > mortality risk

• Long history of fainting
  • + VVS
    • Sheldon 2013 Prog Cardiovasc Dis
    • However, things can change over time/aging...

• Multiple episodes
  • < risk
    • In BrS patients predictive of negative EPS (>6 100%NPV)
      • Krol 1987 JACC
Differentiation between channelopathy syncope, neurogenic syncope and seizures.

<table>
<thead>
<tr>
<th>History</th>
<th>Channelopathy</th>
<th>Neurogenic</th>
<th>Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before episode</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precipitant</td>
<td>Exercise, auditory stimulus, swimming</td>
<td>Prolonged standing, fear, emotional stress, pain</td>
<td>Sleep deprivation, repeated stimuli</td>
</tr>
<tr>
<td>Presyncope</td>
<td>Sometimes</td>
<td>Often</td>
<td>Rare</td>
</tr>
<tr>
<td>Relationship of episodes to posture</td>
<td>None</td>
<td>Usually standing</td>
<td>None</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Rare</td>
<td>Sometimes</td>
<td>None</td>
</tr>
<tr>
<td>Prodrome</td>
<td>Presyncope</td>
<td>Warmth, diaphoresis, nausea, visual blurring</td>
<td>Aura</td>
</tr>
<tr>
<td>Onset</td>
<td>Sudden</td>
<td>Usually gradual</td>
<td>Sudden</td>
</tr>
<tr>
<td><strong>During episode</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>Seconds to minutes</td>
<td>Usually less than a minute</td>
<td>Variable, can be longer than several minutes</td>
</tr>
<tr>
<td>Seizure activity</td>
<td>Rare</td>
<td>Rare</td>
<td>Always</td>
</tr>
<tr>
<td><strong>After episode</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to complete recovery</td>
<td>Seconds to minutes</td>
<td>Minutes</td>
<td>Minutes to hours</td>
</tr>
</tbody>
</table>
Physical Examination

• Congenital sensorineural deafness (*Jervell and Lange-Nielsen syndrome*)
  • Jervell 1956 Am Heart J

• Dysmorphic features of *Andersen-Tawil syndrome*
  • short stature, hypertelorism, broad nose, low-set ears and a hypoplastic mandible
  • syndactyly in rare pediatric patients
    • Andersen 1971 Acta Paediatr Scand
    • Marks 2005 JACC

• Signs of trauma – suddenness of the event

• Bite marks
  • anterior part of the tongue
    • caused by hitting the jaw during syncope
  • lateral part of the tongue
    • point to epileptic seizures
      • Adler 2015 Cardiol Clin
B. ECG

- Key aspect!

- **Positive findings** = further evaluation

- **Negative findings** do not exclude these syndromes
  - if the medical history is suggestive = further evaluation is still warranted
B. Examples
Case I

Male aged 12

Syncope while on exertion
Case II

Male aged 35

Syncope with seizure

Temperature 39°C on arrival to A&E
Case III

Girl aged 10

Syncope with swimming
Case IV

Man aged 20

Syncope without prodrome while at rest

Family history of SD in cousin aged 14
C. Hereditary Arrhythmogenic Syndromes
1. LQTS

- QTc 400ms mean in general population
  - Gray zone in between (Schwartz score is helpful if > 450/460ms)
- QTc 480ms mean in LQTS

- Minimal positive for Schwartz score - 450/460ms
  - 10% FP from normal population
  - Still miss 10% of LQTS patients
  - Cutoff of 480ms raises sensitivity to nearly 100% (but lowers specificity)
    - Taggart 2007 Circulation
    - Sy 2011 Circulation

- >500ms bad prognosis
  - Sauer 2007 JACC
### LQTS: Diagnostic Criteria

<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      |
| B Congenital deafness          | 0.5    |

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

#### Score

- ≤1 point: low probability
- 1.5–3 points: intermediate probability
- ≥3.5 points: high probability.

Schwartz 2012 Circ Arrhythm Electrophysiol
ECG phenotype / genotype correlation

LQT1  LQT2  LQT3
Diagnosis

- ECG of Relatives
- Exercise testing
  - Borderline cases
  - QT fails to shorten or lengthens
  - QT stays prolonged after exercise

- In children and <21y 30% - ventricular arrhythmias
  - 9% unsustained torsades de pointes
  - 1% sustained monomorphic VT

Garson 1993 Circulation
Diagnostic Adjuncts

• Epinephrine challenge

• ECG Lying down / Standing

• Holter monitoring
Rationale for Genetic Testing

• Confirming / Excluding Diagnosis (usually AD)

• Prognostic Implications

• Therapeutic Implications
  • Gen + Phen – individuals should be considered for BB (IIa B ESC) as 10% risk of events

• Possibility of gene-specific therapy
  • LQTS 3
    • ↑Na⁺ blockade
    • ↓B-blockers

• Research purposes / gain further knowledge
2. Long QT Syndrome (LQTS) *Expert Consensus Recommendations on LQTS Diagnosis*

1. LQTS is diagnosed:
   a. In the presence of an LQTS risk score $\geq 3.5$ in the absence of a secondary cause for QT prolongation and/or
   b. In the presence of an unequivocally pathogenic mutation in one of the LQTS genes or
   c. In the presence of a QT interval corrected for heart rate using Bazett's formula (QTc) $\geq 500$ ms in repeated 12-lead electrocardiogram (ECG) and in the absence of a secondary cause for QT prolongation.

2. LQTS can be diagnosed in the presence of a QTc between 480–499 ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation and in the absence of a pathogenic mutation.
2. Brugada syndrome (BrS)

- Considered one of the *J wave syndromes*

- Several clinical and genetic similarities with Early Repolarization (ER) syndrome

- The region generally most affected in BrS is the anterior RVOT
  - in ER it is the inferior region of the LV
ECG patterns

Type-1

≥ 2-mm J-point elevation, coved type ST-T segment elevation and inverted T-wave in leads V1 and V2.

Type-2

≥ 2-mm J-point elevation, ≥ 1-mm St segment elevation, saddleback ST-T segment and a positive or biphasic T-wave.

Type-3

Same as type 2, except that the ST-segment elevation is <1 mm.
Placement of pre-cordial leads in higher intercostal spaces can unmask the Brugada ECG pattern.

<table>
<thead>
<tr>
<th></th>
<th>4th ICS</th>
<th>3rd ICS</th>
<th>2nd ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1</td>
<td><img src="V1_4thICS.png" alt="EKG" /></td>
<td><img src="V1_3rdICS.png" alt="EKG" /></td>
<td><img src="V1_2ndICS.png" alt="EKG" /></td>
</tr>
<tr>
<td>V2</td>
<td><img src="V2_4thICS.png" alt="EKG" /></td>
<td><img src="V2_3rdICS.png" alt="EKG" /></td>
<td><img src="V2_2ndICS.png" alt="EKG" /></td>
</tr>
<tr>
<td>V3</td>
<td><img src="V3_4thICS.png" alt="EKG" /></td>
<td><img src="V3_3rdICS.png" alt="EKG" /></td>
<td><img src="V3_2ndICS.png" alt="EKG" /></td>
</tr>
</tbody>
</table>
3. Brugada Syndrome (BrS)  *Expert Consensus Recommendations on Brugada Syndrome Diagnosis*

1. BrS *is diagnosed* in patients with ST-segment elevation with type 1 morphology $\geq 2$ mm in $\geq 1$ lead among the right precordial leads $V_1$, $V_2$, positioned in the 2nd, 3rd or 4th intercostal space occurring either spontaneously or after provocative drug test with intravenous administration of Class I antiarrhythmic drugs.

2. BrS *is diagnosed* in patients with type 2 or type 3 ST-segment elevation in $\geq 1$ lead among the right precordial leads $V_1$, $V_2$ positioned in the 2nd, 3rd or 4th intercostal space when a provocative drug test with intravenous administration of Class I antiarrhythmic drugs induces a type I ECG morphology.
Drug challenge

• Done in pts with a) resting ECG type 2 or 3 Brugada pattern and having FH of SCD < 45 yrs and/or b) FH of type 1 Brugada pattern ECG

• Drugs used

  Flecainide : 2 mg/kg over 10 min iv or 400 mg PO

  Procainamide : 10 mg/kg over 10 min iv

  **Ajmaline** : 1 mg/kg over five minutes iv

  Pilsicainide : 1 mg/kg over 10 minutes iv
Ajmaline

• Na\(^+\) channel blocker (IA V.W. class)

• Half-life 5 mins

• If BrS, it will result in the appearance of a Brugada pattern
  • potent sodium channel blocker
  • short-half life

  • allowing for diagnostic testing as a day case.
Other Options

• Fever
  • Saura 2002 PACE

• Meal-provocation test
  • Ikeda 2006 JCE
3. CPVT

- Mutations affecting genes involved in intracellular Ca2+ regulation.

- Syncope and SCD tend to be the result of adrenergically-mediated arrhythmias, induced by emotional stress or exercise.

- Among 51 patients with CPVT, ER was present in 45% vs. 5-13% in the general population.

- A history of syncope in 78% of those with ER vs. 39% without ER (p=0.005).

  - Tülümen 2016 Europace
3. CPVT

- **Exercise test**
  - PVCs
  - followed by the appearance of couplets
  - NS polymorphic or bidirectional VT
    - Leenhardt 1995 Circulation

- **Adrenaline test**
  - IV bolus of epinephrine (0.1 \( \text{ug/kg} \))
  - Continuous infusion of epinephrine (0.1 \( \mu \text{g/kg/min} \)) for 5 min.

  - A 12-lead ECG
    - before the bolus / immediately after the bolus administration / at 30s intervals during the continuous infusion.
    - Monitor surveillance was present throughout the test and for at least 15 min after stopping the infusion to monitor for the possible occurrence of TdP

  - BP was also monitored at 2-min intervals.

  - The effect of epinephrine on the RR and QT intervals reaches **steady-state at approximately 2–3 min** after the start of the epinephrine infusion.
    - Clur 2010 Pediatr Cardiol
Adrenaline Provocation Test

Monomorphic PVCs

Polymorphic VT

Bi-directional VT

termination of adrenaline infusion

Mok 2006 CMJ 2006
4. Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) *Expert Consensus Recommendations on CPVT Diagnosis*

1. CPVT *is diagnosed* in the presence of a structurally normal heart, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic ventricular premature beats or VT in an individual < 40 years of age.

2. CPVT *is diagnosed* in patients (index case or family member) who have a pathogenic mutation.

3. CPVT *is diagnosed* in family members of a CPVT index case with a normal heart who manifest exercise-induced premature ventricular contractions (PVCs) or bidirectional/polymorphic VT.

4. CPVT *can be diagnosed* in the presence of a structurally normal heart and coronary arteries, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic ventricular premature beats or VT in an individual > 40 years of age.
4. Short QT Syndrome

• Rare channelopathy (1/5000 ?) ; AD

• is associated with both syncope and SCD
  • Whether syncope confers a greater risk of SCD is unclear.

• QTc <330ms to 360ms

• Only some patients with short QT are at risk of SCD
  • Gollob 2011 JACC
Gollob Risk score: SQTs

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc, ms</td>
<td></td>
</tr>
<tr>
<td>&lt;370</td>
<td>1</td>
</tr>
<tr>
<td>&lt;350</td>
<td>2</td>
</tr>
<tr>
<td>&lt;330</td>
<td>3</td>
</tr>
<tr>
<td>Jpoint-Tpeak Interval &lt;120 ms</td>
<td>1</td>
</tr>
<tr>
<td>Clinical history*</td>
<td></td>
</tr>
<tr>
<td>History of sudden cardiac arrest</td>
<td>2</td>
</tr>
<tr>
<td>Documented polymorphic VT or VF</td>
<td>2</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1</td>
</tr>
<tr>
<td>Family history*</td>
<td></td>
</tr>
<tr>
<td>First- or second-degree relative with high-probability SQTs</td>
<td>2</td>
</tr>
<tr>
<td>First- or second-degree relative with autopsy-negative sudden cardiac death</td>
<td>1</td>
</tr>
<tr>
<td>Sudden infant death syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Genotype*</td>
<td></td>
</tr>
<tr>
<td>Genotype positive</td>
<td>2</td>
</tr>
<tr>
<td>Mutation of undetermined significance in a culprit gene</td>
<td>1</td>
</tr>
</tbody>
</table>

High-probability SQTs: ≥4 points, Intermediate-probability SQTs: 3 points, low-probability SQTs: ≤2 points.
5. Short QT Syndrome (SQTS)  

**Expert Consensus Recommendations on Short QT Syndrome Diagnosis**

1. SQTS *is diagnosed* in the presence of a QTc ≤330 ms.
2. SQTS *can be diagnosed* in the presence of a QTc < 360 ms and one or more of the following: a pathogenic mutation, family history of SQTS, family history of sudden death at age ≤40, survival of a VT/VF episode in the absence of heart disease.

**Expert Consensus Recommendations on Short QT Syndrome Therapeutic Interventions**

Class I  
1. ICD implantation *is recommended* in symptomatic patients with a diagnosis of SQTS who
   a. Are survivors of a cardiac arrest and/or
   b. Have documented spontaneous sustained VT with or without syncope.

Class IIb  
2. ICD implantation *may be considered* in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.
3. Quinidine *may be considered* in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.
4. Sotalol *may be considered* in asymptomatic patients with a diagnosis of SQTS and a family history of SCD.
- Early Repolarization

• Case control study of idiopathic VF pts
  • VF cases with ER (+ history of syncope) vs. VF without ER

• Haïssaguerre 2008 NEJM
Take Home Messages
Take home messages - I

• Syncope due to channelopathies is potentially lethal.

• FH of SCD in a patient with syncope should always prompt an exhaustive investigation to exclude hereditary arrhythmogenic syndromes.

• Symptoms before or after syncope may raise the suspicion about arrhythmogenic syncope:
  • But need further confirmation.

• Circumstances of syncope can give important clues, and may help in directing further work-up.
Take home messages - II

- **Diagnosis is difficult** and requires thorough testing.

- **The ECG is crucial for the diagnosis**, but a normal ECG does not exclude any of these syndromes
  - + Rhythm testing/monitoring help

- **Exercise, provocative, and genetic testing** provide focused testing.

- **SCD** from channelopathies **is often preventable** with diagnosis.