Sudden Cardiac death of Athlete Due to QT prolongation

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SCD: Definition

"an abrupt unexpected death of C.V cause"

The majority of SCD in athletes occur during or immediately after exercise. Autopsy is very useful in making a definitive diagnosis of the cause of SCD. Autopsy diagnosis of Long QT require detailed biochemical and genetic studies.

Causes of Sudden Death in 387 Young Athletes

Table 1. Causes of Sudden Death in 387 Young Athletes.

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of Athletes</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>102</td>
<td>26.4</td>
</tr>
<tr>
<td>COMMOTIC cardiomyopathy</td>
<td>77</td>
<td>19.9</td>
</tr>
<tr>
<td>Coronary-artery anomalies</td>
<td>53</td>
<td>13.7</td>
</tr>
<tr>
<td>Left ventricular hypertrophy of indeterminate</td>
<td>29</td>
<td>7.5</td>
</tr>
<tr>
<td>Cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td>20</td>
<td>5.2</td>
</tr>
<tr>
<td>Ruptured aortic aneurysm (Marfan's syndrome)</td>
<td>12</td>
<td>3.1</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>11</td>
<td>2.8</td>
</tr>
<tr>
<td>Tunnelled (bridged) coronary artery</td>
<td>11</td>
<td>2.8</td>
</tr>
<tr>
<td>Aortic-valve stenosis</td>
<td>10</td>
<td>2.6</td>
</tr>
<tr>
<td>Atherosclerotic coronary artery disease</td>
<td>10</td>
<td>2.6</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>9</td>
<td>2.3</td>
</tr>
<tr>
<td>Mysomists mitral-valve degeneration</td>
<td>9</td>
<td>2.3</td>
</tr>
<tr>
<td>Asthma (or other pulmonary condition)</td>
<td>8</td>
<td>2.1</td>
</tr>
<tr>
<td>Heart stroke</td>
<td>6</td>
<td>1.6</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>Other cardiovascular cause</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>3</td>
<td>0.8</td>
</tr>
<tr>
<td>Cardiac sarcoidis</td>
<td>3</td>
<td>0.8</td>
</tr>
<tr>
<td>Trauma involving structural cardiac injury</td>
<td>3</td>
<td>0.8</td>
</tr>
<tr>
<td>Ruptured cerebral artery</td>
<td>3</td>
<td>0.8</td>
</tr>
</tbody>
</table>

LQTS: Introduction

- SCD in young athlete is common presentation of genetic arrhythmia syndromes

- The most common of these syndromes is LQTS, characterized by QT prolongation and an increased risk of SCD, usually due to VF

- Physical stress and emotional stress are common triggers of syncope or SCD in LQTS

- Occasionally these events are triggered by loud noises or occur while the person is at rest
Forms of the Long-QT Syndrome

- Many mutations in 10 genes linked to LQTS have been identified.

- Mutations in three genes, each encoding a cardiac ion channel that is important for depolarization, account for the vast majority of cases; the resulting genetic subtypes are called LQT1, LQT2, LQT3.

- Most families with the condition have their own mutations, which are often termed “private” mutations; an emerging body of data suggests that the location of the altered amino acid (or acids) within the ion-channel proteins may affect the prognosis.

- Some clinical features such as QT morphologic characteristics, the response of the QT interval to exercise, triggers of arrhythmia, and the response to therapies vary according to the disease-associated gene.

Common Forms of the Long-QT Syndrome

<table>
<thead>
<tr>
<th>Variable</th>
<th>LQT1</th>
<th>LQT2</th>
<th>LQT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-associated gene</td>
<td>KCNQ1</td>
<td>KCNH2</td>
<td>SCN5A</td>
</tr>
<tr>
<td>In vitro effect</td>
<td>Decreased $I_{Kr}$</td>
<td>Decreased $I_{Kr}$</td>
<td>Increased plateau $I_{Na}$</td>
</tr>
<tr>
<td>Setting of arrhythmia</td>
<td>Emotional or physical stress, swimming, diving</td>
<td>Emotional or physical stress, sudden loud noise</td>
<td>Rest, sleep</td>
</tr>
<tr>
<td>Typical resting ECG</td>
<td>Broad T wave</td>
<td>Low-amplitude T wave with notching</td>
<td>Long isoelectric ST segment</td>
</tr>
<tr>
<td>ECG at onset of arrhythmia</td>
<td>No pause</td>
<td>Pause</td>
<td>Not established</td>
</tr>
<tr>
<td>QT change with exercise</td>
<td>Failure to shorten</td>
<td>Normal</td>
<td>Supranormal</td>
</tr>
<tr>
<td>QT shortening with mexiletine</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical response to beta-blockers</td>
<td>Less than 15% response</td>
<td>Uncertain</td>
<td></td>
</tr>
</tbody>
</table>

*ECG denotes electrocardiogram, $I_{Kr}$ the rapid component of the delayed rectifier current, $I_{Na}$ the slow component of the cardiac delayed rectifier current, and $I_{Na}$ the cardiac sodium current.*

Electrocardiographic Patterns in the Three Common Forms of the Long-QT Syndrome

Spontaneous VF IN a LQTS patient


LQTS (cont)

• **Torsades de pointes VT VF** causes SCD in LQTS pts

• The LQT3 form of the syndrome can also be associated with *bradycardia*, and slow heart rates may cause syncope

• Most cases are associated with the *autosomal dominant* form (i.e., the Romano–Ward syndrome), with striking variability in clinical phenotypes among mutation carriers; this is called *variable penetrance*.

• Transmission is *not strictly mendelian*; an excess of mutation carriers — especially female mutation carriers — has been reported among the offspring of mutation carriers

• Syncope and SCD is unusual in patients older than 40 years.

LQTS: Some Acquired Causes

• Electrolytes imbalance e.g. hypocalcemia

• Hypothyroidism

• Drugs e.g. antiarrhythmic agents such as sotalol and dofetilide, haloperidol, methadone, and pentamidine

• Most drugs that cause torsades de pointes block the rapid component of the delayed rectifier current (IKr)

• Congital long-QT syndrome, may be discovered in 5 to 20% of drug-induced torsades de pointes patients
LQTCS : Clinical Diagnosis

- Palpitations, presyncope, syncope, and SCD are the presenting *symptoms*.
- *Asymptomatic* persons may be evaluated because the diagnosis is established or suspected in a family member.
- *DD* includes causes of syncope; ranging from V.V syncope to HCM and idiopathic VT.
- *History* can help with the differential diagnosis and point toward specific subtypes of the long-QT syndrome.
- The physical examination and echocardiography (or magnetic resonance imaging are *normal*).

### Schwartz scoring system

<table>
<thead>
<tr>
<th>ECG findings*</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. QT,$^\dagger$</td>
<td></td>
</tr>
<tr>
<td>≥480 msec,$^v^2$</td>
<td>3</td>
</tr>
<tr>
<td>460-470 msec,$^1/2$</td>
<td>2</td>
</tr>
<tr>
<td>450 msec,$^1/2$ (in males)</td>
<td>1</td>
</tr>
<tr>
<td>B. Torsade de pointes$^\dagger$</td>
<td>2</td>
</tr>
<tr>
<td>C. T-Wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>D. Notched T-wave in three leads</td>
<td>1</td>
</tr>
<tr>
<td>E. Low heart rate for age$^\dagger$</td>
<td>0.5</td>
</tr>
</tbody>
</table>

#### Clinical history

- A. Syncope$^\dagger$
  - With stress | 2
  - Without stress | 1
- B. Congenital deafness | 0.5

#### Family history

- A. Family members with definite LQTS$^\dagger$ | 1
- B. Unexplained sudden cardiac death below age 30 among immediate family members | 0.5

Schwartz et al; Circulation 1993;88:782-784
LQTCS : Clinical Diagnosis

- A detailed *family history* is essential. not only a history of SCD, but also drowning, the sudden infant death syndrome, and the death of a family member while he or she was driving (a potential manifestation of syncope).

- *Exercise testing* can be useful to assess the response of the QT interval but arrhythmias are very rare. The *epinephrine* challenge has been used to identify mutation carriers in families with the LQT1 mutation.

- Holter monitoring and electrophysiological testing are generally not useful.

LQTS : Genetic testing

- LQTS is a *clinical diagnosis*, but genetic testing may provide additional information.

- Genetic testing for the common subtypes of the long-QT syndrome is *now available commercially*, and it can identify a mutation in 75% of probands in whom the diagnosis appears to be certain on clinical grounds.

- A *negative genetic* test does *not rule out* the diagnosis. There is also the potential for false positive results, since detection of a previously undescribed mutation does not establish the diagnosis.
LQTS : Genetic testing

• Genetic testing is most useful in two settings. First, when a clinical diagnosis is relatively certain, knowing the specific gene affected may clarify the prognosis and guide therapeutic choices.

• Second, in a family with an affected proband and a known genetic defect, the genotyping of family members can help rule out the diagnosis in some persons.

• However, a positive test identifies a family member as being a mutation carrier, even if he or she is asymptomatic, has a normal QT interval, and is unlikely ever to have an event.

• Genetic testing has not been evaluated in patients who present with a borderline QT interval, and no relevant family history. In these patients, the incidence of false positive and false negative results and their implications for management remain unknown.

LQTS Risk Stratification

• The most powerful predictor of risk is the QTc.

• the incidence of syncope or SCD by 40 years of age in those with a QTc (<446 msec) is less than 20%, whereas it is more than 70% among those in the (>498 msec).

• Associated early depolarization abnormalities were recently found to indicate increased SCD risk and poor prognosis.

• Some data also suggest that pts with cardiac arrest rather than syncope as the presenting symptom are at higher risk for SCD.
Associated early depolarization abnormalities

LQTS: Therapy

- Persons with a very low risk of sudden death (e.g., elderly mutation carriers with normal QT intervals) need **No Tts**, although, it is prudent to avoid drugs known to prolong the QT interval.

- The mainstay of therapy for the long-QT syndrome is **beta-blockade**, whose efficacy is assessed by blunting of the exercise heart rate (e.g., by >20%); beta-blockers do not shorten the QT interval.

- Extensive data before and after the identification of disease-associated genes have **shown superior survival** among symptomatic patients who received beta-blockers (or occasionally among those who underwent left stellate ganglionectomy).

- Data have suggested that syncope or SCD is less likely during beta-blocker therapy among patients with the **LQT1** subtype (10% by 40 years) than among those with LQT2 or LQT3; these findings are consistent with the **adrenergic dependence of LQT1.**
LQTS : Therapy 2

- **Sodium-channel blockers** e.g. mexiletine and flecainide may normalize the QTc interval in patients with the LQT3 subtype.

- However, **Na blockers** may also increase the risk of SCD in pts with overlapping Brugada syndrome; their role as primary therapy in LQT3 thus remains uncertain. Identification of pts with both the LQT3 and Brugada syndrome may require further study (e.g., with the use of ECGs after monitored sodium-channel blocker challenge).

- The use of **ICDs** is widely considered in patients at high risk for SCD including those with **symptoms before puberty**, those with very long QTc intervals (e.g., >500 msec), and those with **syncope**, despite adherence to an adequate **beta-block**ing regimen.

Guidelines for Management of the Long-QT Syndrome

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of Evidence</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No participation in competitive sports</td>
<td>I</td>
<td>Includes patients with the diagnosis established by means of genetic testing only</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>I</td>
<td>For patients who have QTc-interval prolongation (&gt;460 msec in women and &gt;440 msec in men)</td>
</tr>
<tr>
<td></td>
<td>IIa</td>
<td>For patients with a normal QTc interval</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>I</td>
<td>For survivors of cardiac arrest</td>
</tr>
<tr>
<td></td>
<td>IIa</td>
<td>For patients with syncope while receiving beta blockers</td>
</tr>
<tr>
<td></td>
<td>IIb</td>
<td>For primary prevention in patients with characteristics that suggest high risk; these include LQT2, LQT3, and QTc interval &gt;500 msec</td>
</tr>
</tbody>
</table>

Clinical Case

• After SCD of a 13-year-old girl while she was playing basketball, her family went to the clinic for medical evaluation.

• Her parents' resting (ECGs) are normal, but her 9-year-old sister's ECG showed long QT interval.

• There is a history of recurrent syncope in female relatives of the maternal grandmother, but there is no family history of other SCD, sudden infant death, drowning, or death from a motor vehicle accident.

• How should these family members be further evaluated and treated?

Family Tree and ECG Findings of 13yrs Athlete SCD victim and Her Family

Panel A, Family Tree and ECG Findings of the victim (black circle) and Her Family, the orange circle denotes her sister. Numbers indicate (QTc).

Panel B shows mother's lead II before and after exercise. The QT interval, showing the "failure to shorten" that is typical of the LQT1 form of the disease.

Panel C shows the sister's QT interval in lead II.

Conclusions and Recommendations

- Evaluation of family members after SCD should start with a detailed **family history** to elicit information about any other cases of SCD as well as sudden infant death syndrome, drowning, and motor vehicle accidents.
- **Autopsy** findings are usually **normal** in patients with fatal long-QT syndrome.
- If the proband has survived a cardiac arrest, imaging to rule out structural diseases is also **normal**.
- The key to diagnosis is the resting **ECG**; although a long QT interval suggests the syndrome, other causes of QT prolongation (e.g., hypocalcemia or hypothyroidism) should be ruled out.

Conclusions and Recommendations

- Occasionally, the diagnosis will become apparent only with **provocation** such as treadmill exercise or an epinephrine challenge.

- Once the diagnosis of the long-QT syndrome has been established, further history, especially the **circumstances** surrounding the syncope or SCD, and occasionally features of the ECG and **genetic testing** may assist in identifying a subtype.

- Genetic testing is also useful to establish or rule out the diagnosis in a family member of a patient with a known genetic mutation.
Conclusions and Recommendations

- **Beta-blockade** with a long-acting agent is the mainstay of therapy

- The use of an ICD should be considered, particularly when features suggesting an unusually high risk of SCD are present; these features include especially long QT intervals, the onset of syncope with sudden noise or at rest, and certain ECG patterns.

- In the family described, **beta-blockade** is indicated in the 9-year-old sister and the mother (who is 39 years of age and carries the LQT1 mutation).

- The use of an ICD may be considered in the 9-year-old girl because she has one high-risk feature (QTc interval >500 msec), but this approach remains controversial, reflecting the challenges in managing this condition.

Thank You