Family screening after sudden cardiac death: where and how to look?

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DISCLOSURES: None
Family screening for juvenile SCD

- When there is a clinically unexpected sudden death the first evaluation is the cascade from the victim to his/her family.
  - 1) Autopsy reports are critical to define whether structural heart disease is present, if there are cardiac or coronary arteries malformations/abnormalities.
  - 2) Unfortunately autopsy is performed in a minority of cases and it results normal in about 10% of cases but up to 40% (Med J Aust. 2004).
  - 3) Need to retrieve and inspect carefully all the medical charts of the victim.
Age-specific risk and causes

- **High Risk:**
  - Myocarditis
  - HCM
  - LQT
  - ARVD
  - Brugada
  - CPVT

- **Advanced heart disease:**
  - CAD
  - Cardiomyopathies

Risk Increase per year

- 0.1%
- 10-25%
- 0.001%

Adolescents/young adults vs. General population

Age (years)
Causes of SCD in the young

Athletic field SCD

- Structural normal (3%)
- Cardiomyopathy (52%)
- Aortic aneurysm/dissection (4%)
- Anomalous coronaries (19%)
- Atherosclerotic CAD (2%)
- Valvular disease (6%)
- Myocarditis (3%)
- Other structural cause (10%)

Italian SCD

- Structural normal (6%)
- Cardiomyopathy (24%)
- Aortic aneurysm/dissection (5%)
- Anomalous coronaries (10%)
- Valvular disease (11%)
- Myocarditis (10%)

American military recruits SCD

- Structural normal (40%)
- Cardiomyopathy (9%)
- Myocarditis (12%)
- Valvular disease (1%)
- Anomalous coronaries (19%)
- Atherosclerotic CAD (9%)
- Other structural cause (8%)

Tester et al.
Curr Opin Cardiol 2006
On a **clinical ground**, family investigation (n=23 families) revealed probable ARVC in 2, LQTS in 1, and Brugada syndrome in 1.

Overall **clinical** screening of the family members allowed to identify a possible cause of death in 4/23 families (17%)

Skinner JR et al HRJ Dec 2010
Cardiological evaluation (ECG at rest, exercise, or during flecainide challenge echo and Holter), identified the underlying disease in **17 of 43 families (40%)**. The diagnosis was more likely to be made in families in which more surviving relatives were examined and in those with 2 SUD victims who were 40 years of age.

**Tan HL Circulation 2005**
Can we use genetics to explain unexplained sudden death?
Genetic testing in SCD cases and family members

- Genetic screening of 16 genes (HCM genes, 3 LQTS/BrS/SQTL (KCNQ1, KCNH2, SCN5A)) was carried out.
- Genetic screening allowed to unmask four possibly pathogenic mutation carriers in the 49 SCD cases considered.
- Carriers of mutation represent 9% (2/23) of the probands with structural anomalies found after autopsy and 7% (1/14) of those with structurally normal hearts. One mutation in a resuscitated cardiac arrest.
- Eleven additional mutation carriers were found among family members.

Allegue C Int J Legal Med. 2007
Yield of Molecular Autopsy

- dHPLC or direct sequencing of LQT genes 1, 2, 3, 5, and 6 was performed, in a National New Zealand protocol, in SUDY victims aged 1-40.
- 33 cases underwent genetic testing (age at death 18 months-40 years; median 25 years).
- 18 (55%) died during sleep or at rest, 7 (21%) during light activity.
- Rare missense variants in LQT genes were found in 5 cases (15%, CI 3-27%)
  - T96R in KCNQ1 (11 yr old male), P968L in KCNH2 (32 yr old female), P2006A in SCN5A (34 yr old female) and R67H and R98W in KCNE1 (17 and 38 yr old females, respectively).

Skinner JR et al HRJ Dec 2010
HOW MANY SUDS CASES ARE CAUSED BY GENETIC DISEASES?

FROM THE CONSENSUS DOCUMENT OF HRS/EHRA:

- *if postmortem genetic testing was to be performed routinely, the best current estimates are that*
- 25 – 35% of SUD cases from age 1 – 35 years
Sudden infant death syndrome (SIDS) is the term used to refer to unexplained sudden deaths amongst infants under the age of 1 year.
Yield of molecular autopsy

Tester et al.  
Curr Opin Cardiol 2006

Percentage (%)

SUDS (N = 49)  
35%

SIDS (N = 100)  
7%
Genetic studies in SIDS cases collectively suggest that up to 15% of SIDS cases may stem from an underlying genetic channelopathy

(FROM: HRS EHRA GUIDELINES 2011)
Screening of family members of SCD cases

- Once a proband is identified, a family pedigree needs to be expanded as far as possible in order to:
  - Identify family members potentially at risk for the disease and life-threatening events.
  - Reassure non carriers whenever a mutation is identified.
Expert Consensus Recommendations

1. For all SUDS and SIDS cases, collection of a tissue sample is recommended (5-10 ml whole blood in EDTA tube, blood spot card, or a frozen sample of heart, liver, or spleen) for subsequent DNA analysis/genetic testing.
2. In the setting of autopsy negative SUDS, comprehensive or targeted (RYR2, KCNQ1, KCNH2 and SCN5A) ion channel genetic testing may be considered in an attempt to establish probable cause and manner of death and to facilitate the identification of potentially at-risk relatives and is recommended if circumstantial evidence points towards a clinical diagnosis of LQTS or CPVT specifically (such as emotional stress, acoustic trigger, drowning as the trigger of death).
3. **Mutation-specific genetic testing** is recommended for family members and other appropriate relatives following the identification of a SUDS-causative mutation in the decedent.
Genetic testing in family members

WHEN

- the autopsy is negative
- Genetic screening on the victim is not possible or not conclusive
- .......genetic testing of family members is an option

.........or not?
Long QT Syndrome
n=546

- 64% Positive Genotyping: 195 patients, 8,418 cost
- 14% Positive Genotyping: 137 patients, 37,565* cost
- 2% Positive Genotyping: 2 patients, 221,400\(^\wedge\) cost
- 40% Positive Genotyping: 326 patients, 13,402 cost

Cost Per One Positive Genotyping (US$):
- CD-LQTS: 8,418
- PD-LQTS: 37,565
- IVF-FMSCD: 221,400\(^\wedge\)
- ALL LQTS: 13,402

Rong B et al Circulation EP 2010
Brugada Syndrome
N=798

% of Patients

CD-BrS
21,441

PD-BrS
60,872*

IVF-FMSCD
130,500^

ALL BrS
33,148

Cost Per One Positive Genotyping (US$)

0
50,000
100,000
150,000
200,000
250,000

Negative Genotyping
Positive Genotyping
Cost Per One Positive Genotyping

Rong B et al Circulation EP 2010
Rong B et al Circulation EP 2010
Yield and cost per positive genotyping of the screening of HERG, KCNQ1, SCN5A, RYR2, CASQ2, KCNE1, KCNE2 in IVF/FMSCD.

Rong B et al. Circulation EP 2010
Genetic testing in family members

- **WHEN**
  - the autopsy is negative
  - Genetic screening on the victim is not possible or not conclusive...

Genetic testing in family members has a low success rate and therefore is very expensive
Conclusions

- When dealing with an unexplained sudden death it is important to:
  - 1) Request and autopsy
  - 2) save tissue/fluids of the victim for genetic testing
  - 3) clinically evaluate family members

- IF NO DIAGNOSIS IS ACHIEVED:
  - 1) perform genetic testing on DNA of the victim
  - 2) is there is a positive result apply cascade screening in family members

- IF GENETICS ON THE VICTIM IS NEGATIVE:
  - 1) consider screening of family members knowing that yield is very low