The Role of the Autonomic Nervous System in SIDS and SADS

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Voluntary Attention
Frontal Lobe
• Frontal and orbital frontal areas,
• Medial frontal lobe,
• Dorsalateral frontal area, and
• Premotor cortex

Involuntary Attention
• Reticular formation and
• Medulla oblongata
Sympathetic Parasympathetic
Does the ANS play a role in SIDS?

Provide a **smoke-free** environment before and after your baby is born.

**Breastfeeding** can protect your baby.

Always place your baby on his or her **back to sleep**, at naptime and night time.

Provide your baby with a **safe sleep** environment that has a firm surface and no pillows, comforters, quilts or bumper pads.

Place your baby to sleep in a **crib, cradle or bassinet next to your bed**.
Sudden Infant Death Syndrome in History

1st description of SIDS comes from the Old Testament

“Judgment of Solomon”
Sudden Infant Death Syndrome Timeline

1 BC

“Overlying” believed to be sole cause of SIDS

1188

SIDS punishment for refusing to participate in crusades

1291 Germany

Official dictum forbids women from taking infants < 3 to their bed

1733

“Arcuccio” device

Russell-Jones 1985
Sudden Infant Death Syndrome Timeline

1800’s: SIDS attributed to drunkenness or carelessness of mother

1889: Status thymico lymphaticus

1924-47 US: Theory of thymus irradiation leading to SIDS

1965: British government proposes 3 causes: suffocation, infection, hypersensitivity

Jacobs Radiology 1999; Russell-Jones 1985
Sudden Infant Death Syndrome Today

Environmental risk factors:
- Smoking
- Soft bedding
- Prone or side sleeping
- Prematurity

Genetic risk factors:
- 5-HTT polymorphism
- ANS polymorphism
- Cardiac ion channel polymorphism
- Complement or interleukin polymorphism

Impaired autonomic regulation and arousal

SIDS

Moon Lancet 2007
**TRIGGER**
- Exercise
- Emotional Stress
- Sleep
- Medication

**BIOLOGICAL SUBSTRATE**
- Abnormal Repolarization
- REENTRY CIRCUITS
- Disordered Calcium Handling

**THE THIRD FACTOR**
- Autonomic N.S.
- Electrolytes
- Perfusion
- Environment
- ?
Sudden Infant Death Syndrome Incidence

Wilders ISRN Cardiology 2012
(a) Three-four week embryo showing primary brain vesicles

Lateral view of right side

(a) Three-four week embryo showing primary brain vesicles

(b) Seven-week embryo showing secondary brain vesicles

(c) Eleven-week fetus showing expanding cerebral hemispheres overgrowing the diencephalon

(d) Brain at birth (the diencephalon and superior portion of the brain stem have been projected to the surface)
Table 1. Protein-changing variants for 92 SIDS and 92 control subjects

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>Amino acid effect*</th>
<th>SIDS (no. of cases with variant)</th>
<th>Controls (no. of cases with variant)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rare polymorphisms (Total)</td>
<td>Common polymorphisms (Total)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>White Black Total</td>
<td>White Black Total</td>
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<tr>
<td>BMP2</td>
<td>T570A</td>
<td>S190R</td>
<td>1 0 1</td>
<td>0.32 0.070 0.19</td>
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<tr>
<td></td>
<td>C287A</td>
<td>T96K</td>
<td>1 0 1</td>
<td>0.071 0.046 0.059</td>
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<tr>
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<td>G35A</td>
<td>R12H</td>
<td>1 0 1</td>
<td>0.036 0.012 0.023</td>
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<tr>
<td></td>
<td>C166A</td>
<td>L56M</td>
<td>1 0 1</td>
<td>0.27 0.28 0.26</td>
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<tr>
<td></td>
<td>C1157T</td>
<td>A386V</td>
<td>0 1 1</td>
<td>0.071 0.046 0.059</td>
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<td>G1253A</td>
<td>R418Q</td>
<td>1 0 1</td>
<td>0.071 0.046 0.059</td>
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<tr>
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<td>G2071A</td>
<td>G691S</td>
<td>1 0 1</td>
<td>0.071 0.046 0.059</td>
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<td>A2147C</td>
<td>K716T</td>
<td>0 1 1</td>
<td>0.071 0.046 0.059</td>
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<td>C1022T</td>
<td>T341I</td>
<td>0 1 1</td>
<td>0.071 0.046 0.059</td>
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<tr>
<td></td>
<td>A1060G</td>
<td>T354A</td>
<td>0 1 1</td>
<td>0.071 0.046 0.059</td>
</tr>
<tr>
<td></td>
<td>G152A</td>
<td>R51H</td>
<td>0 1 1</td>
<td>0.071 0.046 0.059</td>
</tr>
<tr>
<td></td>
<td>G196T</td>
<td>P66S</td>
<td>0 4 4</td>
<td>0.071 0.046 0.059</td>
</tr>
<tr>
<td></td>
<td>C196T</td>
<td>T240I</td>
<td>0 1 1</td>
<td>0.071 0.046 0.059</td>
</tr>
<tr>
<td></td>
<td>C986A</td>
<td>T329K</td>
<td>0 1 1</td>
<td>0.071 0.046 0.059</td>
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</tbody>
</table>

Genes involved in early development of the autonomic nervous system

Weese-Mayer Pediatr Res2004
SIDS and ANS polymorphisms

Schwartz NEJM 1998
Fig. 1. Heart rates of control (CT) and SSIDS (SS) infants over time for all states combined (left) and sleep states only (right). Note the more rapid decrease in heart rate between 2 and 3 months of age for the control infants.

SS = SIDS infants
CT = controls
“Smart Sock Hopes to Prevent Sudden Infant Death Syndrome”
Can we learn from the common faint?
Investigations

• Normal sinus ECG

• Normal 24hr Holter

• Normal heart sounds, no murmurs

• Normal exercise test

....Diagnosis?
Incidence of syncope across a lifespan

![Graph showing the incidence of syncope across different age groups for women and men. The graph indicates a higher incidence of syncope in older age groups for both genders.]
Dysautonomia arrhythmogenesis

Goldstein Ann Intern Med 2002
When to worry about syncope

- Occurs during exertion without time to stop activity
- Syncope without typical prodromal symptoms
- Occurs when sitting or lying down
- Syncope without a clear/reproducible trigger
- FHx of sudden cardiac arrest/death, or an inheritable arrhythmia
- Abnormal ECG
Syncope in SADS

• 10 yo girl with syncope and seizures while swimming
  ➢ Prior to fainting: presyncope, dyspnea
  ➢ Regained consciousness within 10s without resuscitation

• Remarkable family history:
  ➢ Father with episodes of syncope since 10 yo
Swimming and LQTS

Table 2: Clinical details and outcome for 10 children with long QT syndrome having water-triggered cardiac events

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age at first symptom (years)</th>
<th>Age at water-related event (years)</th>
<th>Age at diagnosis (years)</th>
<th>Event presentation</th>
<th>Resuscitation</th>
<th>QTc (ms)</th>
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<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>Underwater syncope at private pool</td>
<td>No</td>
<td>560</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>7</td>
<td>14</td>
<td>Underwater syncope during swimming race</td>
<td>No</td>
<td>482</td>
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<tr>
<td>3</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>Syncope plus seizure after swimming in lake</td>
<td>No</td>
<td>700</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>Underwater syncope during swimming race</td>
<td>No</td>
<td>520</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>10</td>
<td>8</td>
<td>Underwater syncope during swimming race</td>
<td>No</td>
<td>520</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>Underwater syncope, near drowning</td>
<td>No</td>
<td>460</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>Near drowning, VT arrest in private pool</td>
<td>Yes CPR and DCC</td>
<td>570</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>10</td>
<td>Posthumous</td>
<td>Syncope after swimming underwater</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>5 and 36</td>
<td>22</td>
<td>Underwater syncope plus collapse at hot pools</td>
<td>No</td>
<td>570</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>Slipped through a flotation ring</td>
<td>No</td>
<td>590</td>
</tr>
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</table>
ANS Modulation

Carotid Baroreceptor Stimulation

Cervical Vagal Stimulation

Spinal Cord Stimulation

Renal Sympathetic Denervation

Stellate Ganglion sympathectomy

Transcutaneous Vagal Stimulation
ANS Modulation

<table>
<thead>
<tr>
<th>Stress</th>
<th>Yoga-Based Practices</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Sympathetic Nervous System (SNS)</td>
<td>↑ Parasympathetic Nervous System</td>
</tr>
<tr>
<td>↑ Hypothalamic-pituitary-adrenal Axis</td>
<td>↓ Hypothalamic-pituitary-adrenal Axis</td>
</tr>
</tbody>
</table>

Streeter Med Hypotheses 2012
Left cardiac sympathetic denervation

Indicated:

- As second line of therapy for CPVT, LQTS
- Failure of B-blocker therapy
- Occurrence of appropriate ICD shocks
## Left cardiac sympathetic denervation

Table 1: Patient characteristics, LCSD secondary prevention: Summary of patients who received an LCSD at our institution as secondary preventative therapy

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age at LCSD (years)</th>
<th>Genotype</th>
<th>Prior failed therapies</th>
<th>QTc Pre/Post (ms)</th>
<th>No. events/ACA/ICD shocks before LCSD</th>
<th>No. events/ACA/ICD shocks since LCSD</th>
<th>Length of follow-up (months)</th>
<th>Complications from LCSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>2 mo</td>
<td>LQT−</td>
<td>Beta-blockers, lidocaine, mexiletine</td>
<td>651/645</td>
<td>1</td>
<td>0</td>
<td>40</td>
<td>Transfusion**</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>42</td>
<td>LQT2</td>
<td>Beta-blockers</td>
<td>584/560</td>
<td>15</td>
<td>1</td>
<td>30</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>1</td>
<td>LQT−</td>
<td>Beta-blockers, lidocaine, flecainide, mexiletine</td>
<td>451/494</td>
<td>1*</td>
<td>0</td>
<td>27</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>7 mo</td>
<td>LQT2</td>
<td>Beta-blockers</td>
<td>477/464</td>
<td>2</td>
<td>0</td>
<td>26</td>
<td>None</td>
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<tr>
<td>5</td>
<td>M</td>
<td>6</td>
<td>JLNS1</td>
<td>Beta-blockers</td>
<td>507/440</td>
<td>1</td>
<td>2</td>
<td>23</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>3 mo</td>
<td>LQT3</td>
<td>Beta-blockers, lidocaine</td>
<td>687/575</td>
<td>1.5 TdP/day</td>
<td>1.4 TdP/day</td>
<td>21</td>
<td>None</td>
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<tr>
<td>7</td>
<td>F</td>
<td>16</td>
<td>CPVT</td>
<td>Beta-blockers, mexiletine</td>
<td>N/A</td>
<td>10</td>
<td>0</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>1</td>
<td>LQT−</td>
<td>Beta-blockers</td>
<td>529/444</td>
<td>1</td>
<td>0</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>9</td>
<td>LQT1</td>
<td>Beta-blockers</td>
<td>500/498</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>4</td>
<td>LQT−</td>
<td>Beta-blockers, mexiletine</td>
<td>546/598</td>
<td>16</td>
<td>0</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>15</td>
<td>JLNS1</td>
<td>Beta-blockers</td>
<td>562/512</td>
<td>40</td>
<td>0</td>
<td>4</td>
<td>None</td>
</tr>
</tbody>
</table>
ANS and Other Arrhythmias

LQTS

J wave Syndrome

Shen 2014
ANS and Other Arrhythmias

Brugada Syndrome

C  Baseline  Isoproterenol  NE + propranolol  Edrophonium

Shen 2014
Closing thoughts

• ANS plays a major role in arrhythmogenesis and sudden death
  ➢ Imbalance of the sympathetic and parasympathetic
  ➢ Polymorphisms in genes for ANS development in SIDS
  ➢ Dysautonomia has a profound affect on HR

• Modulation of the ANS can be used to treat arrhythmias
  ➢ LCSD
  ➢ Vagal nerve stimulation, carotid sinus stimulation
Going forward...

• Further study into relations of the ANS and inherited arrhythmias is needed

• Determine if ANS polymorphisms can reliably contribute to risk stratification

• Assess ANS modulation as a potential first line therapy for inherited arrhythmias