Recognizing and managing the fetus with channelopathy

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University of Colorado and Children’s Hospital Colorado

Disclosure: I am a consultant for Philips Ultrasound
(Fetal) Long QT Syndrome: Background

- An inherited channelopathy and the leading cause of sudden arrhythmic death in children and young adults
- Causative in ~10%
  - “normal” IUFDs (Crotti et. al. JAMA 2013)
  - SIDS (Schwartz et. al. Circulation 2007)
  - neonatal epilepsy deaths (Tu E. et al. Brain Pathol 2011)
- Fetal ascertainment is poor even with a + family history
  - Live-born population: 1/2-2500 individuals
  - Fetal population: 1/8658 (Flock U J Mat Fetal Neo Med 2015)
- Most common presentation: sinus bradycardia, a subtle rhythm disturbance often unappreciated to be abnormal
- Even fetuses with signature rhythms of VT and/or 2°AVB
  - Unsuspected, undiagnosed or misdiagnosed
  - Delivered prematurely and/or by C-section

Failure to recognize fetal LQTS is a missed opportunity for primary prevention of life threatening ventricular arrhythmias
1989: First Case of Fetal Bradycardia Recognized as LQTS

“...This report (of the first confirmed case of Romano Ward syndrome diagnosed prenatally) confirms that moderate fetal bradycardia (110-120 bpm) does not indicate fetal distress, but indicates that fetuses should be studied for fetal cardiac conduction defects in the newborn period”

Mother, maternal grandmother and infant had prolonged QTc on ECG

Vigliani M. J Reprod Med 1995
Sinus Rates of Fetal LQTS Subjects

OB definition of bradycardia
More on FHR and LQTS

Winbo A et al. Circ Arrhythm Electrophysiol 2015; 8:805-814

- Retrospective study 3\textsuperscript{rd} trimester (29-41 weeks)
- FHR from 184 fetuses with parental LQT1
- 110 mutation carriers
- FHR varied with number of mutations and disease severity
- Some double mutation carriers had FHR>110 bpm

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143 ± 5
131 ± 10
111 ± 6
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“..the current OB standard for fetal bradycardia is not useful with regards to LQTS…but what FHR should signal the need for what type of follow-up is not yet known.”
A FHR/GA algorithm to identify LQTS before birth

- Never again is HR ascertained as frequently and meticulously as during fetal life
- It is standard of care and doesn’t cost anything extra
- The bradycardia of LQTS disappears in early childhood
- Neonatal ECG screening issues
- International multicenter (12 sites) prospective study of FHR/GA in a high risk population
  - Mother or father must have LQTS mutation
  - 12 lead ECG and genetic testing of infant after birth
Preliminary Results: FHR by GA

KCNQ1

KCNH2

SCN5A

No LQTS mutation
Maybe its more than the FHR/Rhythm?
Other features of fetal LQTS
Mechanical Dysfunction in Extreme QT Prolongation

Himeshkumar Vyas, MD, Patrick W. O’Leary, MD, Michael G. Earing, MD, Frank Cetta, MD, and Michael J. Ackerman, MD, PhD, Rochester, Minnesota; and Milwaukee, Wisconsin

Conclusions: This infantile presentation of QT extremis and cardiac dysfunction provides support for the hypothesis of mechanical perturbations stemming from abnormal repolarization. Future studies are needed to investigate whether or not the typical patient with congenital LQTS exhibits any evidence for mechanical dysfunction.
IRT differentiates immune-mediated 2° from LQTS “2° AVB”

Anti-SSA mediated 2° AVB

LQTS:
IRT longer (105 v. 47.5 ±13.8 ms)
ICT shorter (7 v. 60.9 ± 22.6 ms)

IRT during sinus rhythm

Normal: IRT 40 ms

CALM 2 mutation: IRT 100 ms

KCNH2 mutation: IRT 70 ms
CALM 2 mutation

Cardiac Dysfunction in LQTS

Acherman RJ et al. Right ventricular noncompaction associated with long QT in a fetus with right ventricular hypertrophy and cardiac arrhythmias *Prenat Diagn* 2008; 28: 551–553
Non-invasive ‘gold standard’ for LQTS diagnosis: Fetal Magnetocardiography (fMCG):

- Recorded without direct contact with source (mother)
- Superconducting quantum Interference device (SQUID)
- Unaffected by amniotic fluid or vernix
- Excellent signal to noise ratio
- Limited maternal (signal) interference
- Can be recorded from 18-40 weeks
Results: Genetics of LQTS Rhythms

Circulation. 2013;128:2183-2191

39 referred for fMCG

Red = +family history

8

31 (26)
Sinus Bradycardia
KCNQ1
SCN5A E1784K (1)

5
Fetal TdP + 2° AVB

SCN5A
R1623Q (n=2)
L409P

G628S
T613K

KCNH2

3
Fetal 2° AVB

CACNA1C
G406A

CALM 2

Not tested

31 (26)
Sinus Bradycardia
KCNQ1
SCN5A E1784K (1)
fMCG and LQTS

Can fMCG to diagnose LQTS before birth? YES
- 39 fetuses evaluated 19-38 (29.5 ± 5.2) weeks
  - 27 family history
  - 12 LQTS rhythms (sinus brady, VT, SSA negative 2°AVB)
- No significant difference between fetal/neonatal HR or QTc
- QTc of 490 ms (> 95%) identified LQTS with 89% sensitivity/specificity

Can fMCG risk stratify LQTS before birth? YES
- 2°AV block (KCNH2) (± family history)
  - QTc <600 ms : postnatal SR or transient 2° AV block
  - QTc > 600 ms : postnatal TdP and aborted sudden cardiac death
- Sinus brady (KCNQ1) (usually +family history)
  - QTc ≤ 550 ms: postnatal sinus brady
- TdP (KCNH2, SCN5A R1623Q) (rarely +family history)
  - QTc >600: postnatal TdP
  - Prenatal TdP = postnatal TdP

Circulation. 2013;128:2183-2191
### Success of in utero treatment for TdP based on genotype (n=20)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Magnesium</th>
<th>Beta Blockers</th>
<th>Digoxin</th>
<th>Lidocaine</th>
<th>Mexiletine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RX SUCCESSFUL</strong></td>
<td>6/6*</td>
<td>1/1</td>
<td>2/2</td>
<td>1/1</td>
<td>2/2</td>
</tr>
<tr>
<td><strong>RX PARTIALLY SUCCESSFUL</strong></td>
<td>1/1</td>
<td>3/3^</td>
<td>1/1</td>
<td>1/1</td>
<td>2/2</td>
</tr>
<tr>
<td><strong>RX UNSUCCESSFUL</strong></td>
<td>1/1°</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
<td>1/1</td>
</tr>
</tbody>
</table>

* KCNH2 T613M (2)
KCNH2 G628S (2)
KCNH2 T612L
KCNH2 S624R
KCNH2 L987V

^KCNH2 T612L

°KCNH2 T613M
Fetal Surveillance w. LQTS Family History

- Treat maternal Mg and/or 25,OH Vit D deficiency
- No QT prolonging meds
- Continue maternal BB if mother LQTS +
- fMCG at 24-28 wks

If LQT1 +
- Monthly FHR
- After 32 weeks qo week FHR

If LQT3 +
- Monthly FHR
- After 32 weeks qo week FHR

If LQT2 +
- Monthly FHR
- Between 20-24 weeks:
  - Fetal echo
- After 30 weeks
  - Follow-up fMCG
  - q week non-stress testing
  - qo week fetal echo

- Postnatal ECG and Genetic testing
Treatment algorithm for fetal LQTS TdP and 2° AVB

(Ideally) VT confirmed by fMCG to be TdP or monomorphic VT with prolonged QTc

IV Mg
Loading dose + maintenance infusion

No success
Add IV lidocaine and BB

No success
- d/c lidocaine
- Start mexiletine
- Increase BB dose

Success
Add mexiletine + BB

Hydrops resolve; d/c IV Mg

Success
- Continue IV Mg until no hydrops
- Add mexiletine d/c lidocaine
- Continue BB
- Add po Mg

TdP recurs
- Continue po meds
- Go back to IV Mg

Success
- Continue Mex + BB + add oral Mg
- d/c lidocaine
- Start mexiletine
- Increase BB dose
Future Directions

- Embrace a paradigm shift from post-event recognition of LQTS and secondary prevention to prenatal recognition and primary prevention of ventricular arrhythmia
  - Adopt a population based strategy before birth to most effectively identify individuals at risk for sudden death.
    - Develop an ascertainment technique with high sensitivity/specificity
    - Educate OB colleagues about presentation and in utero LQTS management
    - Improve communication between “pediatric” “adult” and “fetal” cardiologists
- Prevent sudden death in the young by identifying risk of sudden death in the youngest
References


False positive patient

- Genotype negative
- QT interval 440 ms at birth and 1 month
False Negative Patient at 28 weeks

- SCN5A E1784K
- FHRs not < 3rd % for GA, QT interval 430 at birth
- In other sibs QTcs have become longer with age
<table>
<thead>
<tr>
<th>Beta Blocker</th>
<th>Approximate % transfer</th>
<th>Protein Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadolol</td>
<td>Unknown</td>
<td>20-30%</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Fetal ~20% maternal concentration</td>
<td>93%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Fetal and maternal concentrations ~ equal</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Fetal and maternal concentrations ~ equal</td>
<td>10%</td>
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</tbody>
</table>
Conclusions

The clinical profile of LQTS patients with complex fetal arrhythmias is suggestive of mutation type

Fetal TdP and QTc > 580 ms are harbingers of postnatal adverse cardiac events

Fetal treatment can abolish or reduce the incidence of TdP and prolong gestation
In utero treatment of genotype positive LQTS fetuses with VT and 2° AVB

<table>
<thead>
<tr>
<th>Author</th>
<th>GA (wks)</th>
<th>Hydrops/CHD</th>
<th>In utero Rx</th>
<th>Control?</th>
<th>Mutation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuneo ('13)</td>
<td>28</td>
<td>Yes/no</td>
<td>BB, Lidocaine, Mg</td>
<td>No, no, yes</td>
<td>KCNH2 G628S</td>
<td>Alive</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>No/no</td>
<td>BB, Mg</td>
<td>No, yes</td>
<td>KCNH2 T613M</td>
<td>Alive</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>Yes/no</td>
<td>Mg, Lidocaine, Mex</td>
<td>Yes, yes, partial</td>
<td>SCN5A R1623Q</td>
<td>died</td>
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<tr>
<td></td>
<td>30</td>
<td>Yes/no</td>
<td>BB, Mg, Mexilitine</td>
<td>No, yes, partial</td>
<td>SCN5A R1623Q</td>
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<tr>
<td>Flock ('15)</td>
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<td>Yes/yes</td>
<td>Digoxin</td>
<td>No</td>
<td>KCNH2 T613M</td>
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</tr>
<tr>
<td>Miller ('04)</td>
<td>28</td>
<td>yes</td>
<td>BB</td>
<td>No</td>
<td>SCN5A R1623Q</td>
<td>Cardiac transplant</td>
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<tr>
<td>Simpson ('09)</td>
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<td>yes</td>
<td>Flecainide, Mg, BB</td>
<td>No, yes, partial</td>
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<td>Died</td>
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<tr>
<td>PC</td>
<td>29</td>
<td>Yes</td>
<td>Mg, mexilitine</td>
<td>Yes, no</td>
<td>KCNH2 S624R</td>
<td>Alive</td>
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<tr>
<td></td>
<td>24</td>
<td>yes</td>
<td>Mg, BB</td>
<td>Partial, yes</td>
<td>KCNH2 T613M</td>
<td>Alive</td>
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<tr>
<td>PC</td>
<td>27</td>
<td>yes</td>
<td>Mg, Lidocaine</td>
<td>Yes, yes</td>
<td>KCNH2 G628S</td>
<td>Alive</td>
</tr>
<tr>
<td>PC</td>
<td>23</td>
<td>yes</td>
<td>Flecainide, Mg, Mex</td>
<td>No, yes, yes</td>
<td><strong>KCNH2 L987X</strong></td>
<td>Died</td>
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<tr>
<td>PC</td>
<td>29</td>
<td>yes</td>
<td>BB, Mg</td>
<td>Partial</td>
<td>KCNH2 F627L</td>
<td>Alive</td>
</tr>
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### In utero treatment of phenotype positive LQTS fetuses with VT and 2° AVB

<table>
<thead>
<tr>
<th>Author</th>
<th>GA (wks)</th>
<th>Hydrops/CHD</th>
<th>Medication</th>
<th>Control?</th>
<th>Genotype</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hofbeck ('97)</td>
<td>32</td>
<td>yes</td>
<td>Flecainide BB</td>
<td>No Partial</td>
<td>ND</td>
<td>Died</td>
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<tr>
<td>Ohkuchi ('99)</td>
<td>34</td>
<td>yes</td>
<td>Digoxin</td>
<td>No</td>
<td>ND</td>
<td>Alive</td>
</tr>
<tr>
<td>Chang ('02)</td>
<td>26</td>
<td>yes</td>
<td>Lidocaine BB</td>
<td>No Partial Less hydrops</td>
<td>ND</td>
<td>Alive</td>
</tr>
<tr>
<td>Lin ('04)</td>
<td>35</td>
<td>No</td>
<td>BB BB BB</td>
<td>No No No</td>
<td>ND</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>No</td>
<td>BB BB BB</td>
<td>No No No</td>
<td>ND</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>No</td>
<td>BB BB BB</td>
<td>No No No</td>
<td>ND</td>
<td>Alive</td>
</tr>
<tr>
<td>Anuwutnavin ('12)</td>
<td>32</td>
<td>No</td>
<td>BB</td>
<td>Partial</td>
<td>ND</td>
<td>Alive</td>
</tr>
<tr>
<td>Fukushima ('10)</td>
<td>24</td>
<td>No</td>
<td>Mg</td>
<td>yes</td>
<td>ND</td>
<td>Alive</td>
</tr>
</tbody>
</table>
Fetal Surveillance with LQTS rhythm: + or - LQTS family history

- Sinus bradycardia
- 2° AVB
  - fMCG + for LQTS
  - 2° AVB
    - 1X weekly FHR
    - Every 2 week fetal echo
  - Resolution
    - Postnatal ECG
    - Genetic testing
- Ventricular tachycardia
  - Recurrent with heart failure
    - Treat
  - No QT prolonging meds
  - Genetic testing if QTc prolonged
  - Treat maternal Mg and/or 25, OH Vit D deficiency
  - No QT prolonging meds
  - Observation or Treat?
  - Observe or Treat?
  - Rare/Intermittent
    - No heart failure
    - Progression
      - Recurrence with heart failure
        - Treat
      - Continuation
        - Postnatal ECG
        - Genetic testing
And what about that family history?

1. 

2. 
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10

3. 
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10

4. 
- Generation 2: 
  - 1
  - 2
  - 3
  - 4
- Generation 3: 
  - 1, 2, 3: ICD, not tested
  - 4: ICD, not tested
  - 5: + mutation
  - 6: + mutation
  - 7: + mutation
  - 8: ICD and + mutation

KCNH2 L987X

Slide courtesy of Professor Frank Pillekamp MD, Düsseldorf

- = consanguineous
- = dead
- = Misscarriages and unknown gender
- = mutation / pacemaker
- = unborn
Results of in utero treatment for TdP

- **Magnesium**
  - Successful Rx: N=10 (100%)
  - Unsuccessful Rx: N=0 (0%)

- **Beta Blocker**
  - Successful Rx: N=6 (Partial)
  - Unsuccessful Rx: N=0 (0%)

- **Lidocaine**
  - Successful Rx: N=3 (Partial)
  - Unsuccessful Rx: N=0 (0%)

- **Mexilitine**
  - Successful Rx: N=4 (Partial)
  - Unsuccessful Rx: N=0 (0%)
# Fetal LQTS Consortium

Total Enrollment=52 from 8 active sites Complete data from 24 subjects

<table>
<thead>
<tr>
<th><strong>North America</strong></th>
<th><strong>Europe</strong></th>
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<tbody>
<tr>
<td>Children's Hospital Colorado Denver CO USA</td>
<td>Center Cardiac Arrhythmias of Genetic Origin Milan, Italy</td>
</tr>
<tr>
<td>Vanderbilt University Nashville TN USA</td>
<td>The University of Amsterdam, the Netherlands</td>
</tr>
<tr>
<td>University of Utah Salt Lake City UT, USA</td>
<td>Bonn University. Bonn Germany</td>
</tr>
<tr>
<td>University of Rochester, Rochester NY, USA</td>
<td>University of Munster, Germany</td>
</tr>
<tr>
<td>Mayo Clinic, Rochester MN, USA</td>
<td>German Heart Center Munich Germany</td>
</tr>
<tr>
<td>University of Toronto, Ontario, CA</td>
<td>Hospital Bichat-Claude Bernard, Paris, FR</td>
</tr>
<tr>
<td></td>
<td>University of Oslo, Oslo, Norway</td>
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<tr>
<td></td>
<td>Royal Brompton Hospital, London, UK</td>
</tr>
<tr>
<td></td>
<td>University of Helsinki, Helsinki, Finland</td>
</tr>
<tr>
<td></td>
<td>Umea University, Umea, Sweden</td>
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</tbody>
</table>
Presentation of Fetal LQTS

<table>
<thead>
<tr>
<th>Rhythm</th>
<th>N</th>
<th>Geno-typed</th>
<th>Mutation</th>
<th>De Novo</th>
<th>Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus brady</td>
<td>32</td>
<td>26</td>
<td>KCNQ1</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Fetal TdP</td>
<td>4</td>
<td>4</td>
<td>KCNH2</td>
<td>25%</td>
<td>75%</td>
</tr>
<tr>
<td>Fetal TdP + 2° AVB</td>
<td>22</td>
<td>13</td>
<td>(6) KCNH2 (7) SCN5A</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>Neonatal TdP</td>
<td>7</td>
<td>4</td>
<td>(3) SCN5A (1) CALM 2</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>Neonatal TdP + 2° AVB</td>
<td>8</td>
<td>3</td>
<td>(1) KCNH2 (2) SCN5A</td>
<td>100%</td>
<td>0</td>
</tr>
</tbody>
</table>
A FHR/GA algorithm to identify LQTS before birth: Preliminary results

- International multicenter (15 sites) study pregnancies with maternal or paternal KCNJQ1, KCNH2 or SCN5A (fetallqts.com)
  - Review FHR/GA throughout pregnancy
  - Postnatal ECG and genetic testing
- Total Enrollment = 52 from 8 active sites
- Complete data from 24 subjects
Outcome of the Successful Evaluation

• Differentiate between LQTS and no LQTS
• Optimize the in utero environment
  • Normal maternal Mg/Ca, Vitamin D and electrolyte levels
• Don’t give QT prolonging medications (like pitocin or Zofran)
• No premature delivery for non-reactive fetal bradycardia
• Delivery at a cardiac center of excellence
Evaluation of Suspected Channelopathies

Improve ascertainment

The fetus at risk

• FH LQTS
• LQTS rhythm (including bradycardia)

Elucidate the electrophysiology of TdP

*Risk stratify pre/postnatal care*

*In utero management and delivery of the LQTS fetus*
<table>
<thead>
<tr>
<th>Group</th>
<th>QTc (ms) (mean ±SD)</th>
<th>LQTS Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>KCNQ1</td>
</tr>
<tr>
<td>Group 1</td>
<td>*656.8 ± 42.6</td>
<td>0</td>
</tr>
<tr>
<td>TdP (n=7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>552.3 ± 92.4</td>
<td>2</td>
</tr>
<tr>
<td>2° AVB (n=5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>504.2 ± 50.2</td>
<td>21</td>
</tr>
<tr>
<td>Sinus Brady</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- P = 0.001

Other includes uncharacterized, untested, and compound mutations
Summary of Results

TdP or TdP + 2° AV block

- All w. SCN5A had aborted or sudden cardiac death in utero or within the first year of life despite medical +/- pacemaker Rx
- All w. KCNH2 survived w. medical +/- pacemaker Rx