Cardiac Disease in Organic Acidemias

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Introduction to the Heart

• Heart very metabolically active, uses fatty acids as a preferred fuel
• Heart needs fuel for 2 major functions:
  • Muscle contraction (the pump & plumbing)
  • Conduction system (the electrical wiring)

• How to treat muscle and conduction problems
Healthy mitochondria are essential for Heart function
OAs (PA/MMA) and the Heart

1) Risk for developing cardiomyopathy (CM)
   - CM is disease of the heart muscle - abnormal muscle contraction can mean the heart cannot generate enough force to deliver oxygen-containing blood to the body and the brain.

2) Risk for developing prolonged QT interval
   - Prolonged QT disease is an abnormality of the conduction system (the electrical system of the heart - these electrical signals tell the heart when to beat and allow this to happen in an organized way). A prolonged QT can mean a predisposition for developing an arrhythmia, or abnormal electrical conduction.

   - The reason why individuals with PA develop heart muscle and conduction system abnormalities is not known - but we have some ideas...
### Frequencies of signs & symptoms reported in MMA/PA (from Baumgartner et al, Orphanet J Rare Dis 2014)

<table>
<thead>
<tr>
<th>Sign/symptom</th>
<th>MMA</th>
<th>Frequency</th>
<th>PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental delay</td>
<td>25-65%</td>
<td></td>
<td>59-100%</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Frequent during metabolic crises, but no specific data</td>
<td>21-30%</td>
<td></td>
</tr>
<tr>
<td>Hypotonia</td>
<td>No data</td>
<td></td>
<td>56-100%</td>
</tr>
<tr>
<td>Seizures/epilepsy</td>
<td>16-53%</td>
<td></td>
<td>25-53%</td>
</tr>
<tr>
<td>Movement disorder</td>
<td>30-45%</td>
<td></td>
<td>40%</td>
</tr>
<tr>
<td>Metabolic stroke like events &amp; basal ganglia lesions</td>
<td>Up to 35%</td>
<td></td>
<td>&gt;10 cases</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>Single cases</td>
<td></td>
<td>&gt;10 cases</td>
</tr>
<tr>
<td>Neuropsychiatric symptoms</td>
<td>Rare</td>
<td></td>
<td>rare</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>28-47%</td>
<td></td>
<td>4 cases</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Few cases</td>
<td></td>
<td>9-23%</td>
</tr>
<tr>
<td>Prolonged QTc interval</td>
<td>Not reported</td>
<td></td>
<td>37 cases</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>22 cases</td>
<td></td>
<td>7 cases</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>Rare</td>
<td></td>
<td>rare</td>
</tr>
</tbody>
</table>
Case reports of cardiomyopathy in MMA are starting to emerge

• Focus of this talk will be PA as cardiac disease is more prevalent, and better studied
• Discussion of cardiomyopathy can be applied to other (not all) OAs
• Long QT has NOT been observed/reported in MMA or other OAs
CM is a disease of the heart muscle and can come in two forms:

1) Dilated- DCM
Two forms of CM:
2) Hypertrophic Cardiomyopathy - HCM
How do we diagnose cardiomyopathy?

- Echocardiography (ECHO) is the single best test to diagnose and follow CM
- Electrocardiography (ECG or EKG) can be helpful to screen for CM, but cannot diagnose CM
- Other tests can also be used (ex.- cardiac MRI) but are usually not necessary or practical
- Simple tests are also very useful- chest x-ray, some basic blood tests (if organs do not receive enough oxygenated blood they get sick)
CM can be detected by an x-ray:

Normal

Enlarged heart
Echocardiogram: Gold Standard

• Used to make diagnosis
• Follow for changes over time
How does EHCO help the cardiologist? How does it help a patient?

• ECHO is very good for:
  Making a diagnosis
  Detecting subtle abnormalities early in disease
  Following changes over time
  Making objective measurements of heart function (ejection fraction, shortening fraction)

• ECHO is not good for:
  Day-to-day management
  Detecting arrhythmias
What does an ECHO see?

• What a normal heart looks like:
What does an ECHO see?

• What a normal heart looks like:
Dilated Cardiomyopathy: by ECHO
Dilated Cardiomyopathy: by ECHO
Hypertrophic cardiomyopathy: by ECHO
Other ways that CM can be detected:

- **SYMPTOMS:** what parents may notice
  - Fatigue- inability to do the same activities, or tiring more quickly
  - Shortness of breath with activity
  - Weight loss
  - Nausea/vomiting, or early satiety
  - Swelling in face, abdomen, legs
  - Other symptoms may occur but are not typical: chest pain, fainting
How is CM detected?:

- SIGNS: what doctors will notice
  - Increase in heart rate
  - Extra heart sound (gallop, murmur)
  - Pulmonary edema: extra fluid in the lungs
  - Ascites/ Edema (fluid build-up in abdomen or limbs)
  - Liver enlargement
What do these signs indicate:

• HEART FAILURE = pump failure, evidence that heart fails to deliver adequate blood/oxygen to tissues
• Congestive heart failure = pump failure resulting in back-up of blood
  • Left side- backs up into lungs
  • Right side- backs up into body
OTHER TESTS:

• BNP- hormone released by a “stretched” heart
• Blood tests that measure oxygen delivery to organs:
  • Kidney function
  • Lactate
  • Oxygen content of blood going back to heart
  • Liver function
  • Cognitive function
Cardiomyopathy in PA

- CM will be found in 1/4 to 1/3 of PA patients (based on 2 studies of ~20 patients each)
- DCM presents more commonly than HCM in PA
- *Both* Dilated and Hypertrophic CM have been seen
- Both dilated and hypertrophic CM can be seen in the *same patient at the same time*
- Sometimes HCM can turn into DCM
Cardiomyopathy in propionic acidaemia


Medical Unit, Institute of Child Health, London, United Kingdom

- 19 patients
- 5 or 6/19 had some evidence of CM
- 3 died
- 3 had resolution of findings
- Carnitine did not appear to have any affect
Cardiomyopathies in Propionic Aciduria are Reversible After Liver Transplantation

Stephane Romano, MD, Vassili Valayannopoulos, MD, Guy Touati, MD, Jean-Pierre Jais, MD, PhD, Daniel Rabier, MD, Yves de Keyzer, PhD, Damien Bonnet, MD, PhD, and Pascale de Lonlay, MD, PhD. J Pediatr. 2010 Jan;156(1):128-34
(Hopital Necker-Enfants Malades, Universite´ ParisDescartes, Paris, France)

- 20 patients total
- 6 developed cardiomyopathy
- 2 died of cardiac arrest
- 2 received liver transplant and cardiac function improved
- 2 not able to receive liver transplant due to cardiac disease
In PA patients diagnosed with Cardiomyopathy:

- Age at diagnosis: between 5-11 years in French cohort, but may occur as early as 10 months, or as late as adulthood
- CM does not correlate with PCC enzyme activity
- CM does not correlate with metabolic decompensation
- No evidence that Heart function responds to carnitine
- Cardiomyopathy has been treated with both liver and heart transplantation

What can we take from these studies?
- All children with PA should be screened for CM!
- Late onset may occur- screening should not stop in adulthood
Why should a PA (MMA) patient see a cardiologist?

- ECHO can detect subtle abnormalities before symptoms are present
- There are medications that help slow the progression of CM in children and help them feel better
- PA patients with severe CM may be candidates for organ transplantation
- A prolonged QT can also be treated (medications, devices)
- There are many medications that should be avoided in someone with a prolonged QT.
What is a QT??

- The QT is a time interval measured on an ECG (electrocardiogram)
- A QTc is a QT interval that is “corrected” for heart rate
- The QT can be thought of as the time the heart needs to “re-set” itself for the next heart beat.
- When the QTc is too long, dangerous arrhythmias can result leading to collapse and even death.
Long QT syndrome (LQTS)

• THIS IS A DIFFERENT DISEASE
• Caused by mutations in a number of genes that are important for cardiac conduction
• Cardiac conduction = electrical system of heart
• There may be similarities between LQTS and prolonged QT in PA, but they are not the same thing
What an ECG looks like:
What an ECG tells you:

Electrical impulse spreads from Sinus Node throughout Left and Right Atria

Electrical impulse spreads from Bundle Branches throughout Left and Right Ventricles

Sinus Node
Atrioventricular Node
His Bundle
Right Bundle Branch
Left Bundle Branch

QRS Complex
PR Segment
ST Segment

P
PR Interval
QT Interval

R

Q

S

T
Compare normal to prolonged-QT
Prolonged QT in PA

- A study of 10 patients has shown that 70% of PA patients have a prolonged QTc (>440 msec)
- 60% have a QTc >460 msec (longer = more dangerous)
- 4 individuals underwent exercise testing, QTc was longer with exercise (this is very abnormal)
- There are case reports of PA patients having collapse (syncope) related to prolonged QTc
- No infants have been diagnosed with prolonged QTc
- The QTc may prolong with age

**Normal QTc is different for men and women normal for male is <440, normal for female is <460**
Treatment of a prolonged QTc

- Medications *may* be protective:
  - Beta blockers, Magnesium supplementation
  - No treatment specific to PA
- Implantable Cardioverter Defibrillator (ICD)
  - Not benign therapy
How to detect arrhythmia

- ECG
- Telemetry (monitor)
- Holter Monitor
- Event Monitor
- Loop recorder
Loop recorder
Health Supervision Guidelines (for MMA and PA): what the experts say

- Echocardiogram at presentation and every year to evaluate for CM
- Echo as needed to evaluate shortness of breath, tachycardia, or other signs/symptoms of heart failure

- They also say:
- ECG annually to screen for long-QT
- Holter monitor annually (24 hour monitor)
- ECG and Holter if any syncope (fainting) or other symptoms concerning for arrhythmia
Thank you for coming! Questions?
## CM in MMA...

- Prada et al, J Pediatr 2001: “Cardiac disease in methylmalonic acidemia.”

<table>
<thead>
<tr>
<th>Findings</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMA type</td>
<td>Cobalamin B</td>
<td>Mutase&lt;sup&gt;0&lt;/sup&gt;</td>
<td>Mutase&lt;sup&gt;0&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age at diagnosis of MMA</td>
<td>4 months old</td>
<td>Newborn</td>
<td>Newborn</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Ethnic background</td>
<td>Caucasian</td>
<td>Moroccan</td>
<td>Caucasian</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Age at cardiomyopathy onset</td>
<td>22 years old</td>
<td>7 months old</td>
<td>4 years old</td>
</tr>
<tr>
<td>Cardiomyopathy type</td>
<td>Hypertrophic</td>
<td>Dilated</td>
<td>Dilated</td>
</tr>
<tr>
<td>Chest radiography</td>
<td>Cardiomegaly</td>
<td>Cardiomegaly</td>
<td>Cardiomegaly</td>
</tr>
<tr>
<td>Electocardiography</td>
<td>Persistent T-wave inversion</td>
<td>No rhythm abnormalities</td>
<td>Pre-excitation, paroxysmal SVT</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Pericardial effusion, LVEF 18%</td>
<td>LVEF 20%, mild aortic stenosis</td>
<td>LVEF 20%-25%</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td>Vomiting, tachycardia</td>
<td>Feeding difficulties, vomiting, and increased sweating</td>
<td>Respiratory distress and cardiac failure</td>
</tr>
<tr>
<td>Cause of death</td>
<td>Ventricular arrhythmia</td>
<td>Metabolic crisis triggered by gastroenteritis</td>
<td>Progressive cardiomyopathy and respiratory failure</td>
</tr>
<tr>
<td>Age at death</td>
<td>22 years old</td>
<td>2 years old</td>
<td>4 years old</td>
</tr>
<tr>
<td>Family history of sudden death</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
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