Genomics & Modern Health Care
Caring for the Special Children & Adults of Isolated Populations

Propionic Acidemia

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PROPIONIC ACIDEMIA
Why is this a “Disease?”
When & why does the disorder become an “Illness?”
Propionic Acidemia – Basal Ganglial Stroke
his 31 year old Sister, Newly diagnosed with PA and never treated, had an Abrupt Decrease in LVEF 58 > 43% with Sinus Bradycardia, Poor R-wave Progression, depressed ST segments in inferior & lateral leads, QTc 431 msec. She obtained full exercise goal & Cardiac MRI did not show fibrosis.

How should the adult pa cases be Evaluated & managed?
HIGH PLASMA GLYCINE LEVELS CORRELATE WITH DECREASED SF (EF). PLASMA GLYCINE LEVELS PROBABLY CORRELATE WITH PROPIONYL-COA LEVELS IN MITOCHONDRIA.
BACKGROUND

• Propionic acidemia (PA) is one of the most common disorders in Amish & Mennonite populations throughout North America. *PCCB c.1606A>G* is a European variant with significant residual enzyme activity.

• Neonatal presentations are infrequent with this variant. Keto-acidotic crises with recurrent vomiting, tachypnea, encephalopathy, seizures, & metabolic strokes typically develop during infectious illnesses. An injured infant may become acutely hypotonic with poor head and trunk control followed by generalized dystonia. The basal ganglia are targeted & show increased T2-signal with low-diffusion immediately after crisis, then, volume loss, scarring, and worsening hypertonic dystonia.

• At least 30% patients develop heart failure, which often presents at the end of minor respiratory tract illnesses without keto-acidosis. End stage PA heart disease is a dilated, thin wall myocardium with endocardial fibroestosis.
• **PCCB c.1606A>G** has significant residual enzyme activity, blood propionyl-carnitine levels are low. False-negative Newborn Screening by MS/MS is NOT uncommon.

• Propionyl-CoA forms within mitochondria by oxidation of 4 amino acids & odd chain fatty acids. Propionyl-carnitine is formed in mitochondria by an acyl-transferase & propionyl-CoA.

• The propionyl-carnitine levels in myocardium are more than 1000 times higher than blood levels. Amino acids & odd chain fatty acids transported into myocardium & oxidized to propionyl-CoA.

• Urine organic acids by GC/MS have diagnostic levels of methylcitrate. 3-OH-propionate is present. Propionyl-glycine is usually absent. Glycine levels in plasma are high, but, unlike methylcrotonylglycineuria, glycine conjugation in this variant of PA is insignificant as a detoxifying pathway.
EARLY OBSERVATIONS

• Two teenage brothers developed symptomatic cardiomyopathy were treated to lower tissue propionyl-CoA and restore citric acid cycle anaplerosis.

• We routinely monitored cardiac morphology, LV ejection fraction, QTc, selected citric acid metabolites by GC/MS, plasma amino acids by HPLC, propionyl-carnitine by MS/MS, and, more recently, serum Coenzyme Q levels.
Among PA patients LV ejection fraction (64 ± 11%) was lower than controls (73 ± 5%; p<0.0001).

LV-EF <3SD below controls) developed in 12 (36%) PA patients, ranged from mild (EF 58%) to severe (EF 7%).

Heart failure was fatal in three children.

In the 2 brothers with cardiomyopathy LV ejection decreased from normal to 18% and 42%.

On the metabolic therapy outlined above, LV-EF increased from slowly from 18% to 56% over 4-6 months, and, from 42% to 63% over 1 month.
RECOVERY

- Magnetic resonance imaging showed biventricular dysfunction with increased end diastolic volumes but myocardial interstitial volume fraction was normal 26% - no fibrosis.
- After recovery of LV-EF, CMR documented normal biventricular function, cardiac volumes, and absence of fibrosis.
- Myocardial interstitial volume fraction was normal-29%.
- After recovery & on therapy the 17-year-old achieved predicted exercise - a targeted HR of 200 bpm.
- His EKG showed prolonged QTc, which shortened with exercise, and inverted T-waves in V5&6.
BIOCHEMISTRY-2: PROPIONYL-COA

• Propionyl-CoA is a counter-regulatory metabolite. At low concentrations it inhibits Pyruvate Dehydrogenase, slowing entry of glycolytic carbons into the citric acid cycle.

• Propionyl-CoA is an anti-metabolite. It is competitive with acetyl-CoA’s for reaction with oxaloacetate to form citrate.

• 2-Methylcitrate derives from the pathological reaction of propionyl-CoA & oxaloacetate. Methylcitrate is probably a competitive inhibitor aconitase, slowing the conversion of citrate to isocitrate.

• Biochemical pathology of propionyl-CoA is also directly related to failed anaplerotic synthesis of succinyl-CoA and the resulting decreased activity of succinyl-CoA dehydrogenase.
ANAPLEROSES OF THE CITRIC ACID CYCLE

Glucose

- Phosphoenolpyruvate
- Pyruvate

Alanine Cysteine Glycine Serine Threonine Tryptophan

Isoleucine Leucine Tryptophan

Leucine Lysine Phenylalanine Tryptophan Tyrosine

Acetyl CoA ↔ Acetoacetyl CoA

Oxaloacetate

- Asparagine Aspartate
- Aspartate Phenylalanine Tyrosine
- Isoleucine Methionine Threonine Valine

Fumarate

Sucinyl CoA

α-Keto glutarate

Arginine Glutamate Glutamine Histidine Proline

Propionic acidemia
Succinyl-CoA is a critical metabolite. The severity of PA of as a disease may largely reflect the central role of succinyl-CoA in citric acid cycle function.

Ketone body use during fasts and illnesses requires succinyl-CoA as a CoA donor. Pathological ketosis indicates depletion of succinyl-CoA & should be recognized as a marker for impending intoxication.

Succinyl-CoA reacts also with glycine to initiate mitochondrial heme synthesis. Chronic depletion of succinyl-CoA leads to loss of heme-dependent electron transport centers.

Succinyl-CoA dehydrogenase:Coenzyme-Q is Complex-II of the electron transport system. Loss of function means loss of the proton gradient, oxidant damage to & degeneration of mitochondria.

Succinyl-CoA dehydrogenase regulates mitochondrial replication through controlling the activity of NDPK.
SUCCINYL-COA + GLYCINE >>>> HEME SYNTHESIS
COMPLEX-II ETT: Succinyl-CoA Dehydrogenase FADH2 & CoQ-10

Does CoQ or FAD+ depletion cause oxidant damage, long-QTc & CHF?

Electron Transport Chain inside Mitochondria

- NADH reductase
- FeS
- 2e-
- CoQ
- Cyt c
- Cyt b
- Cyt a
- ATP synthetase
- Complexes 1, 2, 3, 4, 5
- NADH + H+
- FADH2
- FAD
- 1/2 O2 + 2e− + 2H+
- H2O
- 3ADP + 3P → 3ATP

Citric Acid Cycle and Fatty Acid Oxidation Occur

C. Ophardt, c. 2003
CoQ10 plasma & cellular concentrations

CoQ10 in plasma (µmol/L) vs. CoQ10 in blood cells (pmol/cellsx10^6)

- White blood cells: p<0.05
- Platelets: p<0.001
Models of the hERG1-potassium channel

Cysteine-723 & Methionine-713 Are oxidant sensitive –SH groups.

Is long-QTc an indication of oxidant damage?
Patients with the Amish/Mennonite variant of propionic acidemia are often stable for many years - undiagnosed and untreated.

The natural tolerance of the disorder likely involves adaptations that limit propionyl-CoA accumulation, supply succinyl-CoA through alternative anaplerotic pathways, and protect the function of succinyl-CoA dehydrogenase:CoQ.

Dietary protein excess, fasts and starvation, biotin, carnitine, CoQ, iron or FAD depletion, hypoxia or drugs that further impair genetically compromised mitochondrial energetics can set-off a cascade of events that lead to acute of energetics in the myocardium or brain and-or mitochondrial depletion.
BIOCHEMISTRY-5: THERAPEUTICS

- Propionyl-CoA accumulation is limited by restriction of dietary protein to 0.75-1.25 g/kg-day, by the administration of carnitine 25-100 mg/kg-day & by limited transport of isoleucine, valine & threonine into the brain and myocardium through competitive LAT-1 amino acid transport kinetics. Effects of therapy are monitored by plasma amino acids, free carnitine & propionyl-carnitine in whole blood, serum CoQ, & the urine citrate/methylcitrate ratio.

- Succinyl-CoA formation & succinyl-CoA dehydrogenase function are supported by supplemented amino acids that form 2-ketoglutarate, fumarate, oxaloacetate, and by K-citrate. The effect of these supplements upon citric acid cycle repletion is monitored by measuring the citrate/methylcitrate ratios in urine using GC/MS.

- Oral glucose, anaplerotic amino acids, and potassium-citrate can be used to prevent or reverse ketosis during illnesses.
Propionyl-CoA accumulation is also limited by the propionyl-CoA cofactor biotin. High-dose biotin 5 mg twice daily is given to stabilize the residual enzyme activity. This vitamin is used with the same rational as a “chaperone” drug. Betaine is being investigated as a possible chaperone drug for propionic acidemia.

The function of Complex-II succinyl-CoA dehydrogenase:CoQ will be compromised if iron, sulphur, riboflavin, niacin, or CoQ deficiencies develops. Serum CoQ levels have recently been found low in several of our PA patients. We now supplement with 100-200 mg/day of CoQ10 and aim to have serum levels 3 times about the upper limit of the normal range.
Acquired long QTc syndrome is seen in the majority of patients but is uncommon in infants & increases with age. The etiology and treatment this acquired long QTc disorder is being studied.

An interesting hypothesis about the cause of acquired long QTc in propionic acidemia is that it arises from oxidation of cysteine & methionine SH groups in hERG1 potassium channel and is a “biomarker” for poor Complex-II function & inadequate myocardial CoQ10 protection.

Studies of the effect of improved anti-oxidant protection upon QTc are in progress.

Sudden cardiac death in this variant of PA is common. Management protocols should be developed to protect at risk PA patents from drugs and dietary compounds that are known to increase the risk of life threatening events.
PREVENTION
EARLY DETECTION BY NEWBORN SCREENING

• In the absence of myocardial fibrosis, the cardiomyopathy of PA may be reversible by nutritional therapy that:
  
  1) limits propionyl-CoA accumulation in mitochondria through dietary protein restriction, high-dose biotin, and carnitine

  2) supports citric acid cycle function through daily intake of citrate, malate, and anaplerotic amino acids

  3) supports mitochondrial complex-2 function by an anaplerotic supply of succinyl-CoA & prevents oxidant damage to mitochondria by use of Coenzyme Q10 & vitamin E
CONCLUSION -1

- Cardiomyopathy is common in patients with the PCCB c.1606A>G variant, p.ASN536ASP. This is a relatively common European variant that was found in 10% of a survey of 55 cases from Central Europe. A single allele conveys a phenotype similar to the Amish/Mennonite phenotype.

- The life-time risk is fatal heart disease is high. Heart failure and arrhythmia cause of untimely death.

- Propionic acidemia should be considered in patients of any age who present with “idiopathic” cardiomyopathy.
CONCLUSION - 2

- Monitoring of heart function by cardiac ECHO & EKG shows sub-clinical myocardial dysfunction and long QTc are present in the majority of patients with this PCCB variant.

- Sustained recovery has been obtained with metabolic therapy. However, extensive myocardial fibrosis seen on cardiac MRI represents end stage disease.

- Myocardial intoxication develops from metabolism of Isoleucine & Valine within myocardial mitochondria – not from free propionate absorbed from the gut or released into blood by the liver.

- A transplanted heart can metabolize amino acids and clear propionyl-CoA normally.
FIRST FIND A MEDICAL HOME FOR PATIENTS WITH PROPIONIC ACIDEMIA, THEN, ACCEPT THE NEED FOR TREATMENT.

• Common infections cause severe metabolic illnesses – prevention, early detection and treatment of infections are essential. **WHO WILL PROVIDE THIS CARE?**

• Ketonuria can be detected by parents and reversed at home. **CONTROL OF VOMITING, ORAL REGIMENS OF GLUCOSE, POLYCITRA, AMINO ACIDS, AND CARNITINE CAN REVERSE KETOSIS.**

• Dietary management can prevent the accumulation of propionyl-CoA & the depletion succinyl-CoA.

• **WHAT ARE THE IMPORTANT BIOMARKERS?**