A "mitochondrial way" of understanding Organic Acidemias

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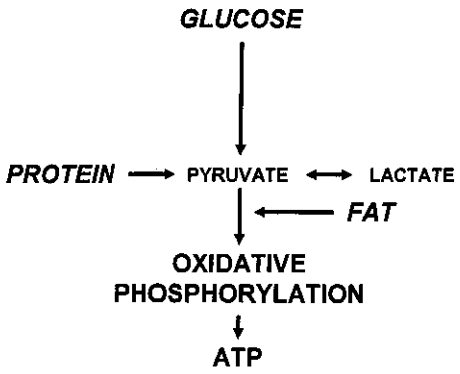
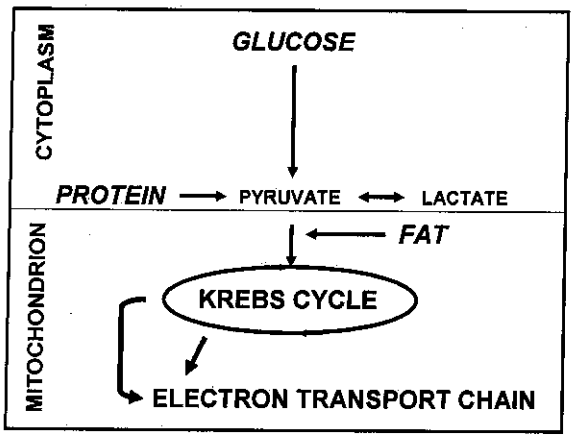




MITOCHONDRIAL DISEASE

- First really described in the 1970s
- Diagnoses "exploded" in the 1990s
- Incidence ~ 1:4000? Perhaps much higher?

MITOCHONDRIAL DISEASE

- Very large class of disorders
- Very wide range of presentations
- Each patient has a unique prognosis

VARIABLE PHENOTYPE

- **M**itochondrial **E**ncephalomyopathy, **L**actic **A**cidemia, and **S**troke-like episodes
- Most common presentation is maternally inherited diabetes and deafness

Patient Katie - Medical history

- Patient Katie was growing and developing well until 18 months when her height began to level off (then 50th centile); by 6 yr - 5th centile. Investigations were not conclusive; she was given the diagnosis of "constitutional short stature"
- Prior to 6 years, Katie was able to run & ride a bicycle without becoming fatigued. Over the next 6 months, she became more exercise intolerant

The onset of mitochondrial disease can occur at any age.

Patient Katie - Medical history

- By 7-1/2 years, strenuous exercise was followed by a headache and vomiting, droopy eyelids & fatigue, requiring a nap. Soon, only minutes of exercise could induce such symptoms
- The night after her 8th birthday party, Katie was found moaning in bed, staring, with tongue hanging out, drooling, incontinent; she felt weak. Taken to the ER - ?seizure. Lactate: 5-6 mmol/L (NL=0.5-2.2)

Patient Katie - Medical history

- Developmental milestones were normal with no history of regression. Performing well at school

The symptoms vary from day to day.

Patient Katie - Medical history

- Several weeks later, Katie was well but had a "busy day". Awoke later - crying, vomiting, headache. Claimed she could not see. She became unresponsive, had several episodes of twitching of both arms, lasting 2-3 minutes
- EEG – no seizures, just diffuse slowing
- MRI scan – symmetrical "bright spots" in the optic nerves
- Ophthalmology - diminished acuity
- All symptoms resolved within days

Mitochondrial disease is progressive.

Patient Katie – Medical history

- mtDNA - mutation at bp3243, indicative of MELAS syndrome.
- MELAS = Mitochondrial Encephalomyopathy, Lactic Acidemia and Stroke-like episodes

Patient Katie – Medical history

Katie suffers from poor stamina or premature fatigue.

She has "good days" and "bad days".

"Bad days" are associated with symptoms that are more intense or persistent.

"Bad days" are triggered by physical exertion, infection, emotional distress, and autonomic stress.

Patient Katie – Medical history

Katie developed acute lethargy associated with migraine

MRI – acute infarctions in the left occipital lobe and parietal lobe, with increased T2 signal in the left thalamus

Patient's lethargy resolved, but had a persistent mild right-sided weakness, and significant defect in her right visual field

CLINICAL FEATURES

- ***NEUROLOGIC (CNS, PNS)***
- ***AUTONOMIC***
- ***EYE***
- ***HEARING***
- ***MUSCLE***
- ***HEART***
- ***LIVER***
- ***KIDNEY***
- INTESTINE
- METABOLIC
- THYROID
- PARATHYROID
- ADRENAL
- PITUITARY
- BONE MARROW
- PANCREAS
- SKIN
- HAIR

Considering Mitochondrial Disease

- Multi-system involvement
  - ***CNS***
    - Dev delays, regression
    - Stroke-like episodes
    - Ataxia
    - Migraine
    - Tremor

Considering Mitochondrial Disease

- Multi-system involvement
  - *HEARING*
    - Neurosensory loss

Considering Mitochondrial Disease

- Multi-system involvement
  - *EYES/VISION*
    - Blurriness
    - Night vision
    - Ptosis
    - Retinal pigmentation

Considering Mitochondrial Disease

- Multi-system involvement
  - *MUSCLE*
    - Fatigue, weakness
    - Pain
    - Myoglobinuria

Considering Mitochondrial Disease

- Multi-system involvement
  - *HEART*
    - Cardiomyopathy
    - Arrythmia

Considering Mitochondrial Disease

- Multi-system involvement
  - *GI*
    - Gut dysmotility

Considering Mitochondrial Disease

- Multi-system involvement
  - *BLADDER*
    - Neurogenic bladder

Considering Mitochondrial Disease

- Multi-system involvement
  - ***– RENAL***
    - Tubular dysfunction

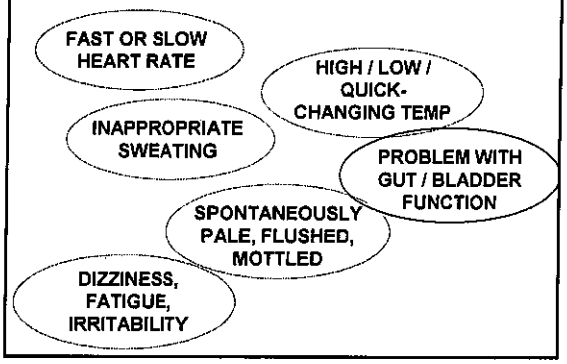
Considering Mitochondrial Disease

- Multi-system involvement
  - ***– ENDOCRINE***
    - Diabetes mellitus
    - Hypothyroidism
    - Adrenal dysfunction
    - Parathyroid dysfunction

Considering Mitochondrial Disease

- Multi-system involvement
  - ***– AUTONOMIC***
    - HR and BP
    - Temperature
    - Skin color
    - Sweating
    - GI and bladder function

AUTONOMIC DYSREGULATION



DIAGNOSIS

- Used to be based mostly on finding an enzyme deficiency (or deficiencies) and/or structural abnormalities on a muscle biopsy

MITOCHONDRIAL DYSFUNCTION

1. ***Genetic syndromes*** (e.g., Prader-Willi syndrome, velocardiofacial syndrome, Rett syndrome, Noonan syndrome, Alstrom syndrome)
2. ***Neurologic syndromes*** (e.g., spinal muscular atrophy, spastic paraparesis variant)
3. ***Metabolic diseases*** (e.g., organic acidemias, fatty acid oxidation defects)
4. ***Medications*** (e.g., Depakote, AZT)
5. ***Malnutrition***

PRIMARY MITOCHONDRIAL DISEASE

vs.

SECONDARY MITOCHONDRIAL DYSFUNCTION

What's the real diagnosis?

- The primary disease process is the PRIMARY DIAGNOSIS.
- Mitochondrial disease/dysfunction is caused by SECONDARY impairment of the mitochondria which may account for (part of) the pathogenesis of the genetic disorder.

Diagnosis

- "Gold standard" – identify a DNA defect known to be associated with mitochondrial disease
- Not possible yet in the majority of cases
- One must build a case for a diagnosis based on:
  - Clinical symptoms
  - Biochemical features
  - Radiologic features (e.g., MRI scan)
  - Mitochondrial structure (tissue biopsy)
  - Mitochondrial function (usually biopsy)
- The more features, the more secure the diagnosis, but there remains a doubt...

Patient Andrew

- Presented after birth with lethargy, poor feeding and vomiting, hypothermia
- Biochemically – metabolic acidosis, high ammonia, ketosis
- Diagnosis – methylmalonic acidemia, mut^0

Patient Andrew

- Fed well initially; became more of a problem after 2-3 years
- No significant metabolic crises; admissions were usually "preventative"
- Developmental delays noted, with hypotonia
- Renal disease developed by 4 years of age

Patient Andrew

- Infections would be followed by a prolonged period of poor feeding
- Gastric emptying slow
- G-tube placed by age 4
- Started to become very fatigued
- More heat and cold sensitive, pale and/or mottled without cause

Patient Andrew

- Heart rate rose and blood pressure dropped; fluctuant, worse in the heat and when sick
- IV fluids helped to stabilize his HR and BP; became more active and his stamina improved
- Feeding rate through the gtube had to run slowly, but improved when IV fluids were given

Patient Andrew

- PICC line was placed because of the frequency of IV fluid therapy → port
- Developed recurrent bouts of sepsis; no significant metabolic decompensation

Patient Andrew

- Because of rapidly progressive kidney disease, underwent liver-kidney transplant at age 5 → liver and kidney function have remained good
- Improvement in GI motility

Patient Andrew

- Because of rapidly progressive kidney disease, underwent liver-kidney transplant at age 5 → liver and kidney function have remained good
- Improvement in GI motility… for about a year

Patient Andrew (now 11 yrs)

- Most significant medical issues are due to autonomic dysfunction:
  - more heat and cold sensitive
  - does not sweat
  - low body temperature
  - without adequate fluids – HR and BP instability
  - Has developed erythromelalgia

Patient Andrew (now 11 yrs)

- Gut motility deteriorated → TPN dependent, now somewhat better
- Pervasive developmental delay
- Seizure disorder, controlled
- Worsening fatigue; impacts his ability to play and learn. He loves his movies, tries to play with other children, and likes to share with others what interests him

Patient Andrew (now 11 yrs)

- Andrew's liver was analyzed:
  - structural abnormalities to the mitochondria
  - defective function of the electron transport chain

Patient Ivanisa

- Presented in the newborn period with vomiting and lethargy
- Associated metabolic ketoacidosis and high ammonia
- Diagnosed with propionic acidemia
- Responded to intervention quickly
- Gtube placed over time to guarantee her nutrition and compliance with medications

Patient Ivanisa

- No severe episodes of metabolic decompensation; 15-20 admissions for mild metabolic instability or as a precaution, responsive to conventional therapy
- Development slowed after 2-3 years and advanced slowly
- Was often the center of attention in a loving family

Patient Ivanisa (now 22 yrs)

- Now has end-stage cardiomyopathy
- Diabetes mellitus
- Has episodes of paranoid psychosis and anxiety; no associated metabolic instability
- Progressive cognitive impairment with increased social withdrawal

Patient Sara

- Presented with severe metabolic ketoacidosis and high ammonia level, along with significant bone marrow impairment
- Diagnosed with propionic acidemia
- Gtube placed at 1-2 years of age for nutrition and medications

Patient Sara

- 2 episodes of significant metabolic decompensation in association with infections; recovered within days – no residual altered neurologic function
- Had about 10 admissions for smaller bouts of instability or as a precaution
- After age 2-3 years, development slowed and progressed slowly

Patient Sara (now 20 yrs)

- Now has stable cognitive impairment
- Fatigues very easily
- Vision deteriorated 4 years ago; optic atrophy diagnosed, now legally blind

Patients Zachary, Gabrielle, and Amani

- Zachary – methylmalonic acidemia
- Gabrielle – propionic acidemia
- Amani – β-ketothiolase deficiency
- All neonatal in onset
- All suffered stroke-like episodes during significant metabolic crises before 3 years of age with severe motor > cognitive deficits

Outcome: Propionic Acidemia

- Early-onset disease carries a worse prognosis but the chronic changes in development are independent of initial management success (Schreiber J, et al, 2012)
- Risk of mortality and acute morbidity reduced with therapy but present
- Risk of mental retardation, focal and general seizures, movement disorders, spasticity or hypotonia, peripheral neuropathy (Surtees et al, 1992; North et al, 1995)

Outcome: Methylmalonic Acidemia

- Early-onset disease generally carries a worse prognosis
- Risk of mortality and morbidity reduced but present
- Risk of mental retardation, seizures, movement disorders, spasticity or hypotonia (Nikolaides et al, 1998)

Pathogenesis

- Effect of severe newborn crisis
- Effect of recurrent metabolic crises
- Inadequate therapy
- Overaggressive therapy
- Chronic toxicity – propionate, ammonia, glycine
- ? Mitochondrial dysfunction

NEW: Cardiomyopathy

- 23% of 27 patients with propionic and methylmalonic acidemia (Romano S et al, 1993)
- 3 patients with MMA and cardiomyopathy in infancy or early childhood (Prada CE, et al, 2011)
- Personal: 4/6 patients with PA above the age of 16-18 years

NEW: Optic atrophy

- Late-onset visual loss, with early profound loss of color vision, and loss of central vision
- Personal – 2/6 above the age of 16 years
- Rats – exposure to propionate → optic atrophy

Comparisons: *Clinical*

Organic Acidemias	***Mitochondrial Disease***
• Developmental delays	• Developmental delays
• Behavioral issues	• Behavioral issues
• Weakness, fatigue	• Weakness, fatigue
• Vomiting/poor feeding	• Vomiting/poor feeding
• Hypotonia	• Hypotonia

Comparisons: *Biochemical*

Organic Acidemias	***Mitochondrial Disease***
• Increased lactate	• Increased lactate
• Abnormal organic acid patterns when well and sick – lactate and pyruvate, Krebs cycle intermediates, 3-methylglutaconic acid	• Abnormal organic acid patterns (variable) – including lactate and pyruvate, Krebs cycle intermediates, 3-methylglutaconic acid

Comparisons: *Radiological*

Organic Acidemias	***Mitochondrial Disease***
• Basal ganglia are susceptible to injury in propionic and methylmalonic acidemia, glutaric acidemia I, isovaleric acidemia, beta-ketothiolase deficiency...	• Basal ganglia, brain stem, and white matter are most at risk for involvement in mitochondrial disease (i.e., Leigh disease variant)

Comparisons: *Radiological*

Organic Acidemias	***Mitochondrial Disease***
• Affected areas show increased peaks of lactate by MR spectroscopy*	• Affected areas often show increased peaks of lactate by MR spectroscopy*

**** Non-specific, and may depend on the stage of the brain lesion.***

Comparisons: *Pathological*

Organic Acidemias	***Mitochondrial Disease***
• During a crisis, may see an enlarged, fatty liver.	• When the liver is involved, it may be enlarged with fat accumulation.

Enzymatic Studies

- Reduced cytochrome oxidase activity in liver in propionic and methylmalonic acidemia (Hayasaka et al, 1982)
- Reduced energy expenditure in patients with propionic and methylmalonic acidemia (Feillet et al, 2000)
- Inhibition of mitochondrial electron transport chain activities in rat brain by methymalonic acid (Brusque et al, 2002)

Enzymatic Studies

- Propionate metabolites may inhibit pyruvate and 2-ketoglutarate dehydrogenase and deplete key compounds in the Krebs cycle (acetyl CoA, oxaloacetate, succinyl CoA) (Schreiber et al, 2012)
- Decreased OXPHOS activity in liver, kidney, heart, muscle in PA and MMA (de Keiser KY et al, 2009)
- Decreased electron transport enzyme activity in MMA mouse model (mut-/-) (Chandler RJ et al, 2009)

Enzymatic Studies

- Cardiac muscle in PA – OXPHOS dysfunction, decreased coenzyme Q10 (Fragaki K et al, 2011)

Promote *Energy* Production

1. Nutrition
2. Adequate and regular rest, including sleep
3. Adequate exercise
4. Vitamins and cofactors may help

VITAMINS & COFACTORS

- Three primary approaches to augmenting energy production:

- **COENZYME Q10**
- **ALPHA LIPOIC ACID**
- **CREATINE**

Mark Tarnopolsky, 2009

Reduce *Energy* Losses

1. Pace physical exertion
2. Acknowledge and treat chronic emotional stress
3. Treat infections, stressors aggressively
4. Keep ambient temperatures comfortable
5. Monitor and treat autonomic dysregulation