Mitochondrial Disease and Dysfunction

MINDD
Sydney, Australia
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www.ihealthnow.org

What Are Mitochondria?

- Present in almost all cells
- Produce energy/ATP for metabolism
  - Decreased ATP production correlates with neuropsychologic and language deficits
  - Minshew et al, Biol Psychiatry, 1993
- Energy metabolism requires oxygen
- Most dependent organs
  - Heart
  - Brain
- Electron transport chain
  - Sequence of events made up of 5 key complexes

Mitochondrial Complexes

- Complex I – NADH dehydrogenase
  - Transfers electron from NADH to CoQ
- Complex II – Succinate dehydrogenase
  - Transfers electron from FADH to CoQ
- Complex III – CoQ – Cytochrome C reductase
  - Transfers electron from reduced CoQ to Cyto C
- Complex IV – Cytochrome C oxidase (COX)
  - Reduces oxygen to H2O, using electron donated from Cyto C
- Complex V – ATP synthase
  - Converts ADP to ATP

Mitochondria

www.mitosoc.org

Mitochondrial Disease

- Mitochondria central to all disease, aging
- Over 1500 gene mutations
- Genetic defect in mitochondrial or nuclear DNA
  - Your mitochondrial DNA are your mother’s
  - Sperm do not donate mtDNA
  - BUT most mito complexes encoded by nuclear DNA
  - SO most genetic defects are autosomal dominant inheritance
- Symptoms vary tremendously
  - Dependent on which organ affected
  - How many mitochondria affected
  - When affected
    - Ming et al, Dev & Develop, 2005
  - How affected
    - Wallace, Genetics, 2008

Case Studies: Abnormal Metabolism, Mitochondrial Dysfunction and Oxidative Stress

Science Sessions (Practitioners)
Sunday 14 August
Dr Nancy O’Hara

www.mindd.org
Mitochondrial Defects

- Electron transport chain
  - Complex I disorder most common
- Substrate utilization
- Citric acid cycle
- Oxidative phosphorylation (OXPHOS)
- Fatty acid oxidation (fats not broken down efficiently)

  - Haas et al, Molecular Genetics & Metab, 2008

Mitochondrial Dysfunction: Some Causes

- Heavy metals (mercury, arsenic, lead, cadmium, aluminum)
- Pesticides, diesel exhaust, PCBs
- Propionic acid from Clostridia
- Oxidative stress/low glutathione
- Hypoxia
- Poor nutrition
- Infection
- Abnormal Proteins (high levels of Alzheimer Beta-amyloid Precursor Protein in ASD)
- Statins

  - Grandjean and Landrigan, Lancet, 2006
  - MacFabe et al, Behav Brain Res, 2007
  - James et al, Am J Clin Nutr, 2004
  - Gutsaeva et al, Neuroscience, 2006
  - Sokol et al, J Child Neurol, 2006

Symptoms of Mitochondrial Disease/Dysfunction

- Many clinical presentations
- Can affect eyes, ears, CV, GI
- Neurologic
  - Movement disorders
    - Posturing, writihng, jerking
  - Hypotonia/hyper tonia
  - Developmental delay
  - Autism
  - Seizures (acute, recurrent, hypoglycemic)
  - Stroke (build up of radicals, changes in blood vessels, "running out of energy")

  - Calvert and Zhang, Pediatr Crit Care Med, 2007

Neurologic Symptoms

- Symptoms due to:
  - Poor utilization of energy
  - Hypoglycemia (brain depends on continual supply of glucose for fuel)
  - Disturbed fat metabolism
  - Disturbed carbohydrate metabolism
  - Increased free radical production
  - Effects of potentially toxic molecules (breakdown products with enzyme defect/deficiency)

- Symptoms
  - Fixed
  - Increased during stress (fasting, infections, exercise)

  - Chauhan et al, Physiopatology, 2006
**Neurologic Symptoms**

**Hypotonia**
- Weak suck and swallow
- Poor head control; floppy
- Drooling
- Hypermobile/hyperflexible joints
- Decreased activity tolerance
- Curved back when sitting
- Difficulty knowing self in space
- Gross and fine motor effects
- Eye-hand coordination poor
- Speech (expressive and receptive)
  ➔ Cohen, Mitochondrial Medicine, 2009

**Seizures**
- Motor
- Sensory
- Autonomic
- Emotional/cognitive
- Marching numbness
- Sense unpleasant odor
- Strange sensation in gut
- Unusual fears
- Flashes
  ➔ Gropman, Mitochondrial Medicine, 2009

**Mitochondrial Symptoms**

**Other**
- GI
  - Dysmotility
  - Pseudo-obstruction and constipation
  - Reflux
- Migraines
- Ptosis, visual loss
- Brief loss of memory
- Pain and cramping
- Diabetes
- Failure to thrive
- SIDS
- Abnormal sweating
  ➔ Goldstein, Mitochondrial Medicine, 2009

**Weakness**

**Mitochondrial Dysfunction and Autism**
- Oliveria et al, Dev Med Child Neurol, 2005
  - Mitochondrial disease in 7% with ASD
  - Dysfunction in 20% with ASD
  - Indistinguishable from other groups of ASD children
- Shoffner et al, Am Acad Neurology, 2008
  - 41 kids with ASD
  - 78% with defects of oxidative phosphorylation
  - Complex I abnormalities most common
  - 75% normal mtDNA
- Poling et al, J Child Neurol, 2008
  - 159 kids with ASD, 94 controls
  - 38% ASD with elevated AST vs 15% controls
  - 47% ASD with increased CK
Mitochondrial Dysfunction and Autism

- Weissman et al, 2008
  - 25 kids with ASD and mitochondrial dysfunction
  - Heterogeneous group but 1:1 gender ratio
  - Multicenter (Cleveland Clinic, MGH, Kennedy Krieger)
  - 96% at least one abnormal lab
  - 68% fatigability, hypotonia
  - 64% GI dysfunction
  - 64% delayed milestones
  - 52% pre/perinatal complications
  - 40% unusual regression, multiple or after age 3 years

Mitochondrial Dysfunction Diagnosis

- Suspicious Labs
  - Isolated elevation of AST or ALT
  - Low glucose
  - Low blood counts
  - Low BUN
  - Low B12 (MMA) and folate (RBC)
  - Low immunoglobulins
  - Evidence of chronic strep or clostridia
  - Evidence of GI dysfunction
    - Haas et al, Pediatrics, 2007

Mitochondrial Dysfunction Evaluation

- Lactate, pyruvate (serum, CSF)
- Ammonia
- Creatinine kinase
- Amino acids (elevated alanine:lysine ratio)
- Organic acids (elevated fatty acid metabolites)
- Carnitine, free and total
- Skin biopsy (fibroblasts – 50% inaccurate)
- Muscle biopsy (histiopath, EM, mtDNA, OXPHOS)
  - Haas, Molecular Genetics and Metab, 2008

Mitochondrial Dysfunction “Sick Labs”

- CMP – Chemistry panel
- Lactate, pyruvate
- Ammonia
- Amino acids, plasma
  - Elevated alanine, as well as glycine, proline, sarcosine, tyrosine
- Urinalysis (ketosis)
- Organic acids, urine
  - Elevated of TCS cycle intermediates, ethylmalonate, 3-methylglucurate and dicarboxylic acids
- Acylglycine, urine
- Acylcarnitine, plasma (suggestive of fatty acid oxidation)
  - Haas et al, Molecular Genetics & Metab, 2008

Mitochondrial Dysfunction Contraindicated Medications

- Aspirin
- Acetaminophen (depletes glutathione by 21%)
- Valproic acid
- Statins (deplete CoQ10)
- Aminoglycosides, gentamicin
- MSG
- Alcohol
- Cyclosporine
  - Waldmeier et al, Molecular Pharmacol, 2002
Mitochondrial Dysfunction Treatment

- No long-term, randomized studies
- "Mitochondrial cocktail"
  - CoQ10
  - Carnitine
  - Riboflavin
  - Antioxidants (vitamins A, C, D, E, ALA, GSH)
  - B vitamins (B12, Folate, thiamine)
  - Creatine
  » Rodriquez et al, Muscle Nerve, 2007

Mitochondrial Dysfunction Treatment

- Carnitine (100 mg/kg/day)
  - Required for entry of long chain fatty acids into mitochondria
  - Spares CoEnzA which gets depleted in mitochondria
  - Increases muscle strength
  - Carnosine
    - Improve language
  - Acetyl-l-carnitine – may improve seizures
    » Tarnopolsky et al, Ann Neurol, 2001

Mitochondrial Dysfunction Treatment

- CoQ10 (10 mg/kg/day)
  - Cofactor (shuttle) involved in electron transfer from complex I and II to complex III
  - Functions as potent anti-oxidant
  - Rationale to bypass Complex I defects
  - Liquid/hydrosoluble formulations better absorbed
  - Antioxidants need to be given in redox couples; give Coq10 with vitamin C
  - 5-15 mg/kg/day with at least 10 mg/kg vitamin C
    » Wallace, Genetics, 2008

Mitochondrial Dysfunction Treatment

- Vitamins E and C
  - Lipid (E) and water (C) soluble anti-oxidant vitamins
  - With mitochondrial dysfunction, free radicals are produced in excess from electron transport chain resulting in oxidative stress
  - Antioxidants given as redox couples (E and C)
  - At least 5-10 mg/kg/day of both vitamins C and E
    » Dobie et al, Pth Neuro-Psychopharmacol, 1993 (dbpc)
  - Vitamin D – 1000-5000 iu/day

Mitochondrial Dysfunction Treatment

- B12
  - Route of entry (SQ, PI, oral)
  - 75 mcg/kg
    » James et al, Neurotoxicol, 2005
- Folate/Folinic acid/L-5-mTHF
  - Leucovorin 2.5 – 5 mg/day at bedtime
    » Moretti et al, Neurology, 2005
- B6 (PSP) and Mg
  » Mosain-Bosc et al, Magnes Res, 2006
- Riboflavin (cofactor for complex II)
  - Bypass complex I defects
  - 2.5 – 5 mg/kg
- Thiamine (cofactor for pyruvate dehydrogenase)
  - Enhances pyruvate entry into mitochondria
  - 2.5 – 5 mg/kg
- Biotin (cofactor in metabolism of fatty acids)
  - 5 – 30 mg/day
  » Tarnopolsky, Mitochondrial Medicine, 2009

Mitochondrial Dysfunction Treatment

- Ginkgo Biloba
  - Modulate mitochondrial apoptosis
    » Smith et al, Cell Mol Biol, 2002
- Chinese herbs
  - Decrease mitochondrial ROS
- HBOT
  - Increases the production of free radicals -> places stress on mitochondria
  - Older and weaker mitochondria are damaged and autophaged
  - Replaced with stronger and healthier mitochondria (natural selection)
  - Upregulate mitochondria (biogenesis)
    » Durante et al, Neurotoxicol, 2006
- Chelation (no data)
- Therapy

Mitochondrial Dysfunction Other Treatment Modalities

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  » B12
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Autism as a Mitochondrial Disease

- Mitochondrial dysfunction and ASD
  - First postulated as cause in 1998
  - Lombard, Med Hypothesis, 1998
  - Disturbance of mitochondrial function and defective oxidative phosphorylation is a subset of ASD
    - Not a chance occurrence
    - Mito dysfunction leads to high ammonia -> neuroglial toxicity
    - This subgroup at greater risk with inflammatory or catabolic stressors including vaccination
    - Responds to high dose antioxidants, mito cocktail and glutathione enhancers

Nick – 3 year old with PDD-NOS

- Many ear infections – frequent antibiotics
- Chronic diarrhea, alternating constipation
- Perseverative behaviors
- Fine motor delays, poor balance
- Poor eye contact
- Decreased pain sensation
- Poor temperature control
- Frequent rashes
- Toe walking
- Fatigue

Nick – Test Results

- Multiple 3+ IgG food sensitivities
- RBC minerals – low calcium, high selenium, high normal arsenic
- CDSA
  - Low lactobacillus
  - 3+ yeast
  - Low SCFA
  - High lactoferrin
  - Low pH
- Colonoscopy – significant blockage
- Clean out, enzymes, SCD without dairy
  - Improved stools
  - Decreased fatigue

Nick - Further Test Results

- Organic acid test
  - Significant yeast markers
  - Multiple Krebs cycle abnormalities
  - High fatty acid metabolites
  - Low pyroglutamic
  - High methylmalonic acid
- Blood work
  - High serum MMA
  - Low free and total carnitine

Nick - Treatment

- Carnitine
  - Increased energy
  - Improved balance
- Antifungals and biofilm protocol
  - Diminished perseverative behaviors
  - Good eye contact
  - No toe walking

Brother born

Nate - History

- Neonatal hyperbilirubinemnia
- Oromotor difficulties
- Hypotonia, significant delays
- Chronic diarrhea
- Excessive fatigue
- Opisthotonus, sandifer’s complex
  - Diagnosed with GERD
  - Treated with Prevacid
Nate – Test results

- High AST (51)
- High lactate (3.8 → 2.0)
- High pyruvate (1.3 → 0.12)
- High ammonia (41 → 28)
- High alanine
- Low carnitine (18 - 26)
- High MMA (1.5)
- Endoscopy
  - Eosinophilic gastritis and duodenitis
- Skin fibroblasts
  - Disturbed oxidative phosphorylation (OXPHOS)
  - Complex I
  - Nick presumptively and subsequently diagnosed

Nate - Treatment

- Carnitine (100 mg/kg)
  - Posture opened up from arched, flexed and fisted to relaxed
- B complex vitamins
  - Able to bear weight
  - Decreased floppiness
- CoQ10 (30-60 mg)
  - Increased energy
- Leucovorin (up to 5 mg)
  - Increased receptive language
- B12 – (75 mcg/kg)
  - Increased expressive language

Nick and Nate – Current Regimen

- Probiotic/saccharomyces boulardii/enzyme
- L-carnitine
- CoQ10
- Biotin
- Folic acid (leucovorin)
- Riboflavin
- Pycnogenol (Trebaticka, Eur Child Adolesc Psychiatry, 2006)
- Typical kids
  - Nate – mild language delay, Carnosine, SPEAK
  - Nick – strep infection, developed tics...

Do not eliminate other diagnoses just because you have one diagnosis

Mitochondrial Pearls

- Speech regression
- Low muscle tone
- Constipation
- Regression with illness, vaccine, exercise
- Low activity level, fatigability
- Low glutathione marker for mitochondrial disorders
  - Symptoms improve as GSH improves (Stanford, 2008)

THINK MITOCHONDRIAL DYSFUNCTION!

Do not go where the path may lead.
Go instead where there is no path and leave a trail...
- Emerson