Metabolic Myopathies
What We Can Learn From Dr Goodwrench

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Disclosure of ABIM Service: Kenneth O'Rourke, MD

- I am a current member of the Rheumatology Board Exam Committee.

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- As is true for any ABIM candidate who has taken an exam for certification, I have signed the Pledge of Honesty in which I have agreed to keep ABIM exam content confidential.

No exam questions will be disclosed in my presentation.
Myopathies

Acquired
- Autoimmune ("idiopathic inflammatory myopathy")
- Inclusion body myositis
- Endocrine disorders
- Drugs / Toxins
- Others
  - Infections
  - Amyloid
  - Paraneoplastic

Inherited
- Muscle channelopathies
  - Cl⁻, Na⁺, K⁺, Ca²⁺
- Muscular dystrophies
  - Limb girdle MD
  - Dystrophinopathies
  - Myotonic dystrophies
  - FSH MD
  - Oculopharyngeal MD
  - Distal MD
  - Congenital MD
- **Metabolic myopathies**
  - Disorders of metabolism (glycogen, lipid)
  - Mitochondrial myopathies
Metabolic Myopathies

Bother?
• Rare
• Referral bias?
  – literature
  – congenital syndromes - pediatrics

Yes!
• Disease-specific implications
• Myositis mimics
• Role of muscle in normal metabolism
  – ~70% body cell mass
  – ~30% resting energy expenditure
Metabolic Myopathies

**Common feature:** impaired production of cellular energy (ATP) in muscle

- Heterogeneous group of diseases
- Hereditary or acquired
- Dynamic or fixed weakness

- “metabolic myopathy”:
  I feel your fear
Objectives

• Discuss the sources of energy for muscle metabolism.

• Describe a systematic diagnostic approach to the patient presenting with a suspected metabolic myopathy, correlating defects in energy production pathways with symptoms and laboratory studies.

• Summarize available therapies for patients with metabolic myopathies.
Analogy: Basic Hybrid Engine

- Cold start
- Limited fuel capacity
- Inefficient
- Pollutes
- Burns better with $O_2$
Analogy: Basic Hybrid Engine

- Efficient
- Rechargeable
- Limited immediate power

Electric
Analogy: Basic Hybrid Engine

- System of shafts, gears, and torque-converters
- to integrate and transmit power
Analogy: Basic Hybrid Engine

- Rapid, max acceleration: Gas
- Fast cruising: Gas
- Slow cruising, or stopped: Electric
Analogy: Basic Hybrid Engine

- Limited fuel capacity
- Inefficient
- Pollutes
- Burns better with $O_2$
Analogy: Basic Hybrid Engine

• Limited fuel capacity
• Inefficient
• Pollutes
• Burns better with O₂
Analogy: Basic Hybrid Engine

- **glucose-6-P**
- **pyruvate**
- **LA**
- **glycogen**
- **Creatine**
- **Cr phosphate**
- **ADP**
- **ATP**
- **Creatine kinase (CK)**
- **Starter**
- **Motor**
- **Cold start**
Analogy: Basic Hybrid Engine

- **glucose-6-P**
- **glycogen**
- **pyruvate**
- **LA**
- **Cr phosphate**
- **Creatine**
- **Creatine kinase (CK)**
- **ATP**
- **ADP**

O2 → **TCA** → ETC & Ox. Phos. → mitochondria
Analogy: Basic Hybrid Engine

- **Electric**
  - Efficient
  - Rechargeable
  - Limited immediate power

- **TCA**
- **β-ox.**
- **ETC & Ox. Phos.**
- **mitochondria**

- **O2**
- **VLDL FA**
- **F-acyl-CoA**

- **glycogen**
- **glucose-6-P**
- **LA**
- **pyruvate**

- **Creatine**
- **Cr phosphate**
- **Creatine kinase (CK)**

- **Efficient**
- **Rechargeable**
- **Limited immediate power**
Analogy: Basic Hybrid Engine

- **glycogen**
- **glucose-6-P**
- **LA**
- **pyruvate**
- **Creatine**
- **Cr phosphate**
- **Creatine kinase (CK)**
- **O2**
- **ETC & Ox. Phos.**
- **ATP**
- **VLDL FA**
- **F-acyl-CoA**
- **β-ox.**
## Metabolic Myopathy:

<table>
<thead>
<tr>
<th>Analogy</th>
<th>Starter</th>
<th>Gasoline</th>
<th>Electric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathway</td>
<td>Creatine Phosphate + free ATP</td>
<td>Glycolysis: Type II fibers</td>
<td>Fatty Acid Oxidation: Type I fibers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anaerobic</td>
<td></td>
</tr>
<tr>
<td>Amount</td>
<td>17 mmols/kg</td>
<td>350 g muscle glycogen</td>
<td>9000 – 15000 g</td>
</tr>
<tr>
<td></td>
<td></td>
<td>440 g glycogen (MM &amp; Liver)</td>
<td></td>
</tr>
<tr>
<td>Exercise duration to exhaust fuel</td>
<td>&lt; 20 seconds</td>
<td>2-3 minutes</td>
<td>many hrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-2 hours</td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td>Most rapid ATP source</td>
<td>Rapid; limited by H⁺ formed</td>
<td>Slow; ATP/O₂ ratio lower than CHO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Limited by O₂ and pyruvate into mito.</td>
<td></td>
</tr>
<tr>
<td>Energy Substrate: Activity</td>
<td>High-intensity, isometric exercise</td>
<td>High-intensity, submaximal exercise</td>
<td>Low-intensity, submaximal exercise</td>
</tr>
</tbody>
</table>
Metabolic Myopathy:

‘Transmission’: electron transport chain (ETC) and oxidative phosphorylation

- ‘Power conversion’: maximizing aerobic metabolism

<table>
<thead>
<tr>
<th></th>
<th>Glycolysis</th>
<th>TCA</th>
<th>ETC &amp; Ox Phos</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP per 1 glucose</td>
<td>2</td>
<td>2</td>
<td>34</td>
</tr>
</tbody>
</table>

- **Highly dependent organs**: skeletal mm, brain, retina, organ of Corti (inner ear), peripheral nerve, endocrine glands, renal tubules
Objectives

• Discuss the sources of energy for muscle metabolism.

• Describe a systematic diagnostic approach to the patient presenting with a suspected metabolic myopathy, correlating defects in energy production pathways with symptoms and laboratory studies.

• Summarize available therapies for patients with metabolic myopathies.
## Pattern Recognition I: Key Questions

<table>
<thead>
<tr>
<th>Key Question</th>
<th>Commonly</th>
<th>Caveat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>exertional weakness/cramping - reversible ± myoglobinuria</td>
<td>some with fixed weakness</td>
</tr>
<tr>
<td>Temporal Evolution</td>
<td>episodic; present at birth or in childhood</td>
<td>some progressive; some present as adult</td>
</tr>
<tr>
<td>Family Hx</td>
<td>many autosomal recessive</td>
<td>mitochondrial myop: some follow maternal transmission</td>
</tr>
<tr>
<td>Precipitants</td>
<td>exercise; infection/fever; eating/fasting</td>
<td>absent</td>
</tr>
<tr>
<td>Assoc’d Systemic</td>
<td>mitochondrial myopathies</td>
<td>Respiratory (GSDII), Cardiac (GSDII, III, XIV), Liver (III)</td>
</tr>
<tr>
<td>Distribution of Weakness</td>
<td>symmetric limb girdle</td>
<td>distal (debrancher), ocular (mito myop)</td>
</tr>
</tbody>
</table>
### Pattern Recognition II: Assess for Changes on Either Side of the ‘Clog’

<table>
<thead>
<tr>
<th>Metabolic Pathway</th>
<th>Upstream, e.g.:</th>
<th>Downstream, e.g.:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycogenolysis/Glycolysis</td>
<td>Muscle biopsy: glycogen accumulation</td>
<td>Lack of lactate rise to anaerobic exercise in some</td>
</tr>
<tr>
<td>Lipid metabolism</td>
<td>Increased FFA: ketones ratio; elevated serum acylcarnitines; Muscle biopsy: fat accumulation</td>
<td>Recurrent hypoketotic hypoglycemia</td>
</tr>
<tr>
<td>Mitochondrial myopathies</td>
<td>Elevated serum lactate, or lactate/pyruvate ratio in some; Muscle biopsy: mitochondrial proliferation (ragged red fibers), often increased SDH staining</td>
<td>Impaired extraction of oxygen from blood: hyperkinetic circulation in exercise; often reduced COX staining</td>
</tr>
</tbody>
</table>
Patient 1: 19 yo female

- 2-3 year history of leg pain, tiredness and weakness, mainly thighs, especially when climbing hills or ascending stairs
- 1 episode of leg giving-way
- No urine discoloration
- FHx: negative
- Exam: normal
- Lab:
  - CK 2564 (< 160), ALT 60
  - CBC, TSH, ESR lactate all normal
  - UA: mod blood, 0-3 RBC/hpf
- PNCV normal
- FIET
  - Lactate (0.5-2.2)
  - NH3 (11-35)
- Muscle biopsy:
  - normal morphology
  - enzyme activity: phosphorylase A: 0.13 umol/min/g (control >12)
Glycolytic / Glycogenolytic Disorders

• Most commonly GSD II, III, V, VII
  – Sx’s: from **brief isometric or less intense but sustained dynamic exercise**
    – sprinting, jogging (several hundred meters), sprinting (30-100 m), ascending stairs/slope
• **Muscle contractures** after exercise
  – not a ‘cramp’
  – unlike neural cramps, cannot be relieved by stretching; doing so is painful!
• **Myoglobinuria** in some
• **The ‘wind’**
  – V (McArdles): **second-wind** phenomena
  – VII (PFK): **out-of-wind** phenomena (additional glucose increases insulin, which then suppresses release of nonesterified fatty acids from adipocytes)
Exercise intolerance, cramps, and myoglobinuria; contractures

V myophosphorylase
VII, phosphofructokinase **
VIII PhK
IX PGK **
X PGAM
XI LDH
XIII beta-enolase

**: hemolytic anemia, as these genes partially expressed in RBCs

Static/Fixed weakness and atrophy; structural and/or toxic damage

II acid maltase
III debrancher
IV brancher
XII aldolase **A
Muscle Phosphorylase Deficiency (GSD V; McArdle’s Disease)

- ~1/100,000; autosomal recessive; >100 mutations of the PYGM gene described...varied clinical expression
- Childhood: mm pain, tightness, easy fatigability
- Teenage: exercise intolerance, cramps, myoglobinuria
- **Adult:**
  - in ~50% diagnosis delayed until age > 40
  - more proximal muscle weakness: in up to 25%, most often those > 40
  - rarely just late-onset weakness, or asymptomatic elevated CK level
- **Post-exertional contractures**
Muscle Phosphorylase Deficiency (GSD V; McArdle’s Disease)

- abnormal FIET: should do non-ischemic protocol
- **chronic CK elevation** (rarely normal, even at rest)
- ‘second wind’ phenomena probably pathognomonic
  - 6-8 minutes into moderate aerobic exercise involving large muscle groups: a marked decrease in early exertional tachycardia
  - Increased uptake of glucose and combustion of fatty acids
  - **NOT seen in other d/o of exercise intolerance**
- **myoglobinuria**
  - > 50%: one episode of pigmenturia; 10% of these have experienced renal failure
- Histology: glycogen accumulation; subsarcolemmal blebs typical
- **Dx:** DNA analysis from leukocytes
Patient 2: 34 yo male

- 4 year history of progressive arm/leg mm pain with activity
- Forearms ‘numb’/painful with manual labor (shipping/rec’g)
- Gave up sports; cannot finish yard work; lies down when gets home
- Pred 60 mg qd: no response
- FHx: male cousin similar sx’s
- Exam: normal
- Lab:
  - CK 1007 (< 160), ALT 51
  - CBC, ESR normal
  - UA: mod blood, 0-3 RBC/hpf

- PNCV normal
- FIET
- Muscle biopsy:
  - normal morphology
  - enzyme activity:
    partial deficiency phosphorylase b kinase (PhK; “McArdle light”)
Forearm Ischemic Exercise Test (FIET)

- Venous blood for measurements of lactate and ammonia, preferably from the nondominant arm without using a tourniquet.
- A blood pressure cuff is inflated around the dominant upper arm and maintained at a pressure either above diastolic, or above systolic pressure (fully ‘ischemic’) while the patient vigorously exercises the dominant forearm by squeezing a tennis ball or a rolled up, partially inflated blood pressure cuff. The cuff is kept inflated around the arm for 2 minutes, or until exercise causes complete exhaustion of the extremity, at which point it is released. CAUTION: compartment syndrome has been reported.
- Two minutes later, repeat lactate and ammonia levels from the dominant arm using a tourniquet.

- **Normal:**
  - minimum 2-3 fold increase over baseline in venous lactate and ammonia.

- **Glycogenoses:**
  - ammonia levels increase but lactate levels remain at baseline
  - except for GSD with fixed weakness: def of acid maltase, phosphorylase b kinase, phosphoglucomutase, or debranching enzyme

- **Myoadenylate deaminase deficiency:**
  - lactate levels increase but ammonia levels remain at baseline.
FIET: Sources of Error

**Lactate**
- Eating, anxiety, hyperventilation may increase lactate
- False positives for lactate (no rise without the metabolic defect): insufficient exercise, case reports of diseases (acute alcoholic myopathy, certain mitochondrial myopathies, MG, PM, thyrotoxic myopathy)
- False negatives (rise in lactate with a metabolic defect): multiple case reports of McArdles; hypokalemic periodic paralysis

**Ammonia**
- on ice to lab in ≤ 15 min
- False negatives (failure to elevate NH3 in absence of primary MADA deficiency): periodic paralysis, flu-like illness, ALS, spinal muscle atrophy, facial and limb girdle myopathy, PM/DM, SLE, PSS, diabetes mellitus, hyperthyroidism, gout

**Common to both**
- > 7 recipes re: ? fasting, BP cuff setting (if at all), exercise duration, timing of samples, what to sample (? pyruvate)
Acid Maltase Deficiency (Pompe’s Disease)

- Classic form: progressive myopathy, death by age 2 from HCM
- Late onset disease may present at any age, even into the 60’s
- FIET normal;
- Adults:
  - progressive proximal + axial weakness - no exercise-related symptoms
  - muscle damage from massive autophagic buildup > weakness/wasting
  - diaphragmatic weakness early, leading to respiratory insufficiency
  - heart and liver not involved
  - smooth mm can be involved late-onset disease

\[ \text{glycogen} \xrightarrow{\text{glucose-6-P}} \text{ac}
\]
Purine nucleotide cycle

Catalyzes the conversion of two ADP molecules into ATP + AMP.

- AMP accumulates during strenuous exercise
- **AMP excess buffered by MADA conversion to IMP, producing NH3**
- MADA activity is in cytoplasm, and is higher in type II, fast fibers
- NH3 stimulates glycolysis by activating phosphofructokinase

1: myoadenylate deaminase (MADA)
MADA Deficiency

- First described 1978 (Fishbein, AFIP)
- ~2% in prevalence in muscle biopsy series
  - The most common metabolic enzyme deficiency in human skeletal muscle
  - Usually compensated for endogenously; patients almost always asymptomatic
- Usually ill-defined, exercise-induced muscle pain, soreness, fatigue, cramps
- Normal or elevated CK; can see myoglobinuria
- Lack of NH3 rise with normal lactate response on FIET
- EMG normal or myopathic
- Secondary in: Duchenne or Becker MD, phosphorylase deficiency, spinal muscular atrophy, ALS
Patient 3: 17 yo male

- 1 year hx of muscle cramps following prolonged (2-3 hrs) strenuous exercise
- Milder exercise asymptomatic
- Occasional associated dark urine during mm cramps
- Hospitalized
  - typical sx’s progressing to immobility
  - cola-colored urine
  - CK > 100,000

- Post discharge:
  - asymptomatic, CK normal
  - Exam: normal
  - **Muscle biopsy**
    - no morphologic abnormality
    - enzymatic activity: **carnitine palmityltransferase**
      pt: 22.89 umol/min/g
      control: >46.6 umol/min/g
Lipid Disorders

- Fatty acid oxidation-dependent: heart, muscle, liver
- Symptoms generally after **prolonged** exercise and prolonged fasting
  - more fixed weakness: carnitine deficiency, ETF def, neutral lipid storage disease
- Usually induced by infection, general anaesthesia, cold exposure (shivering depends heavily on long-chain fatty acids), low CHO/high fat diet
- Do not develop true muscle cramps or contractures
- **No “second wind”**
- **Hypoketotic hypoglycemia** (cannot form ketoacids from fatty acids)
Fatty acid metabolism: carnitine cycle, and beta-oxidation

- Short- and medium-chain FA of less than 10 carbons can cross both the outer and inner mitochondrial membranes.

- Beta-oxidation of fatty acids is mediated by at least 11 enzymes.

Works predominately for C12-C18 chains.

http://quizlet.com/36140260/gi-week-3-lecture-4-fatty-acid-degradation-and-ketone-body-metabolism-flash-cards/
Carnitine palmitoyltransferase II (CPTII) deficiency

- CPT II deficiency is the **most common cause of recurrent myoglobinuria** in both adults and children.
- Incidence ~1 / 291,000
- No correlation between genotype and phenotype
- In 2/3: first intermittent symptoms noted during first or second decade
- **Normal between attacks**

- Prolonged submaximal exercise: myalgias, cramps, muscle stiffness or tenderness, and in some myoglobinuria
- After prolonged exertion
- **No fixed weakness**
- **Also from fasting, cold exposure, viral infections, fever**
- Rhabdo from general anaesthesia, ibuprofen, high doses of diazepam
- **No “second wind”**
Electron Transport Chain: Oxidative Phosphorylation

- Protein subunits of the chain encoded by nuclear and mitochondrial DNA (MtDNA)
- MtDNA inherited only from mother
- Multiple copies of MtDNA / cell
- MtDNA accumulate mutations more than 10x faster than nuclear DNA, and repair is relatively ineffective

<table>
<thead>
<tr>
<th>Complex</th>
<th>Encoded Subunits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>mtDNA</td>
<td>7</td>
</tr>
<tr>
<td>nDNA</td>
<td>38</td>
</tr>
</tbody>
</table>

Coenzyme Q10 (CoQ10, or ubiquinone)

- Fat-soluble quinone
- Transported in HDL/LDL/VLDL
- Localized in hydrophobic portions of cell membranes
- ~ 50% through dietary fat, rest through endogenous synthesis
- **Participates in electron transport during oxidative phosphorylation**
- Antioxidant (muscle cells are postmitotic, and very vulnerable to oxidative stress)
- Regenerates active forms of vitamins C and E

Marcoff L and Thompson PD: J Am Coll Cardiol 49:2231, 2007
Mitochondrial Myopathies

- ~1 / 11-24,000; heterogenous
- **Highly dependent organs**: skeletal mm, brain, retina, organ of Corti (inner ear), peripheral nerve, endocrine glands renal tubules
- **Clinical presentation in adults**: due to defective aerobic metabolism
- **Exercise intolerance**
  - Exaggerated cardiopulmonary response to overcome the block in oxygen utilization
  - Extreme fatigue and **dyspnea at relatively low levels of exertion**
  - no true muscle cramps, no second wind

Figure 1. Clinical features of mitochondrial myopathies, by organ system.

- **Neurologic - central**
  - Ataxia
  - Movement disorder
  - Spasticity
  - Seizures
  - Stroke-like episodes
  - Migraine
  - Encephalopathy
  - Cognitive impairment

- **Neuropsychiatric**
  - Depression
  - Fatigue
  - Psychosis

- **Cardiac**
  - Conduction abnormalities
  - Cardiomyopathy: hypertrophic > dilated

- **Renal**
  - Renal tubular defects
  - Toni–Fanciulli–Debre syndrome

- **Musculoskeletal**
  - Myopathy
    - Skeletal muscle: ocular > axial/proximal > bulbar > distal muscles
    - Smooth muscle: dysphagia
    - Cardiac: cardiomyopathy
    - Myalgia

- **Gastrointestinal**
  - Dysphagia
  - Dysmotility: gastroparesis, diarrhoea, constipation, and/or pseudo-obstruction
  - Hepatic failure

- **Ocular**
  - Myopathy: ophthalmoplegia and/or ptosis
  - Optic atrophy
  - Pigmentary retinopathy
  - Cataract

- **Other**
  - Short stature
  - Spontaneous abortion

- **Endocrine**
  - Diabetes mellitus
  - Hypothyroidism
  - Hypoparathyroidism
  - Gonadal failure
  - Growth hormone deficiency

- **Neurologic peripheral**
  - Axonal polyneuropathy
  - Sensory ataxia
  - Sensorineural hearing loss
  - Autonomic dysfunction
Mitochondrial Myopathies

Clues
• FH, neuro findings, EMG without membrane instability, muscle bx lacking inflam., +ragged red fibers, steroid fail
• Resting lactic acidosis; abnormal lactate/pyruvate ratio

Clinical syndromes
• infantile hypotonia
• Kearns-Sayre: variable myopathic + neuropathic
• isolated proximal myopathy
  – with or without exercise intolerance
  – may have myoglobinuria
  – CK normal or mildly elevated
  – males frequently have hypogonadism
• MELAS: multiorgan involvement (CNS, skeletal/cardiac mm, ophth, GI, renal)
### Evaluation of Suspected Metabolic Myopathy: Symptom Assessment

<table>
<thead>
<tr>
<th>Type of symptoms / signs</th>
<th>Examples:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dynamic:</strong></td>
<td></td>
</tr>
<tr>
<td>– acute and recurrent episodes of irreversible muscle dysfunction</td>
<td>Myophosphorylase</td>
</tr>
<tr>
<td>– some with myoglobinuria</td>
<td>Phosphofructokinase</td>
</tr>
<tr>
<td>– normal between episodes</td>
<td>CPT II deficiency</td>
</tr>
</tbody>
</table>

| **Static:**              |           |
| – proximal weakness, occ’ ly distal or generalized | Acid maltase |
| – respiratory difficulty (resp muscles or cardiomyopathy) | Branching and debranching enzymes |
| – symptoms usually slowly progress | Aldolase |
|                          | Mitochondrial disorders |
Evaluation: Symptom Assessment

Correlate **time course** of muscle symptoms to most likely metabolic process

**Glycogenoses**: from brief isometric exercise, or less intense but sustained dynamic exercise

**Lipid disorders**: after prolonged exercise and prolonged fasting
Evaluation: Lab Features - Myoglobin

**Blood**
- Low MW monomer, not protein bound
- Clearance: renal; and metab to bilirubin

**Urine**
- Visible: excretion > 250 µg/ml
- Supernatant: positive heme in absence of RBC in sediment
- Dipstick sensitivity for detection of rhabdo: ~80%
Evaluation: Lab Features

Creatine kinase (CK)
- In serum at rest and during episodes, with or without myoglobinuria
  - Elevated at rest in McArdle’s
  - CK in CPTII deficiency normal between attacks
  - Marked elevation with normal LDH suggests LDH deficiency

Dicarboxylic acids (DCA)
- In urine – detected in all with intramitochondrial beta-oxidation defects

Lactate and Pyruvate
- In serum: venous lactate may be up in those with mitochondrial myopathies; may see an elevated lactate/pyruvate ratio (normal < 20)

Serum carnitine and acylcarnitines, urine acylglycines and organic acids
- Lipid metabolism defects

Molecular Testing
- By Western blot or by molecular analysis of specific mutations: majority of metabolic myopathies
**Evaluation: Other**

**EMG**
- Exclude neuropathic process
- Support myopathic process
- Spontaneous myotonic discharges:
  - myophosphorylase
  - acid maltase
  - debrancher enzyme deficiencies

**MR spectroscopy and proton MRS**
Evaluation: Muscle Biopsy

• After appropriate blood and urine tests
  – To assist in targeting path evaluation
• Include EM and basic immunohistochemical staining
• Large specimen – freeze for biochemical analysis
  – Talk to your surgeon
Evaluation: Muscle Biopsy

- **Ragged red fibers**
  - > 0-2% under age 50, or >5% at any age, suggest mitochondrial dysfunction
  - A unique feature of mitochondrial myopathies
    - Large collections of mitochondria aggregate in the subsarcolemmal membrane.
    - Stain red or purple with modified Gomori trichrome
    - Mitochondrial activity should be assessed by SDH and CTX-O stain, which show increased SDH and decreased CTX-O activity.
    - Electron microscopic examination will show enlarged, or increased numbers, of crystals or other abnormal morphologic changes

---

**H&E**

**Gomori**

**Subsarcolemmal accumulation**

**Distorted myofibrils leads to ‘ragged fiber edges’**
Cross-section of muscle biopsy from a patient with mitochondrial myopathy (Kearns-Sayre syndrome).

(A) Modified Gomori trichrome stain showing typical **ragged red fiber** (arrow).

(B) Succinate dehydrogenase (SDH) stain showing intense mitochondrial proliferation in “ragged blue” fiber (*).

(C) Serial section of (B) showing that the fiber staining intensely with the SDH **stain lacks cytochrome c oxidase (COX) activity** (*).

*(Courtesy of E. Bonilla, MD, Columbia University, NY.)*

Similar to ragged red fibers, > 0-2% under age 50, or >5% at any age, suggest mitochondrial dysfunction.
Paracrystalline mitochondrial inclusions (EM × 30,000)
(Courtesy of E. Bonilla, MD, Columbia University, NY.)

Represent the crystallized form of dimeric mitochondrial CK under conditions of oxidative stress.
Objectives

• Discuss the **sources of energy** for muscle metabolism.

• Describe a systematic diagnostic approach to the patient presenting with a suspected metabolic myopathy, **correlating defects in energy production pathways with symptoms and laboratory studies**.

• **Summarize available therapies** for patients with metabolic myopathies.
Treatment

- Patient education
- ACR website patient fact sheet
  Practice Management>Clinical Support>Patient Resources>Diseases and Conditions
- Physical therapy: few studies!
  - Immobility shifts muscle metabolism to increasing dependence on glycogen use and reduced capacity for fatty acid oxidation
  - Balancing need to avoid disuse atrophy vs aggravating disease/rhabdomyolysis
  - Resistance (strength; anaerobic) training: most effective for slowing rate of loss of muscle mass and maintaining strength, BUT avoid or perform with caution at low intensity in GSD with dynamic symptoms
    - Aerobic training at < 70% MHR: probably well tolerated
    - Avoid muscle lengthening (eccentric) contractions
- Screen for respiratory involvement

Preisler N et al.
J Inherit Metab Dis (2014)
Treatment - Dietary

Myophosphorylase deficiency

- 37.5 – 75 g sucrose before exercise may improve tolerance
- High protein diet may be beneficial
- Vit B6 supplementation (80% of total pool B6 bound as pyridoxal-phosphate to muscle phosphorylase)

CPT II deficiency

- High CHO (70-75%), low fat (10-15%), low protein (15%)
- MCT oil as a fat source
- Frequent meals
- Extra CHO before sustained exercise, with physiologic stress
- Bezafibrate increases CPT II-mRNA: pilot trial mild form of CPT II def
Treatment - Supplements

- Medical: metabolites and cofactors (electron donors and acceptors, strategies to reduce lactic acid, antioxidants, alternative energy sources)
  
  - **Coenzyme Q10**
    - No pharm. grade supplement
    - No known risks
    - ALS study: safe/tolerable with doses as high as 3000 mg/d for 8 months
  
  - **L-carnitine**
    - To restore free carnitine levels, which are secondarily reduced in patients with resp. chain defects

DiMauro rec at least 400 mg/d (can give total as bid)

Creatine Monohydrate

- Dietary: largely from meat and chicken; most excreted in urine
- Endogenously made in liver and kidney
- Transported freely in blood, enters muscle via active transporter (CreaT)
- Plays role in moving energy (ATP) from mitochondria to cytosol in tissues with high energy requirements (brain, skeletal muscle, heart)
- Has been shown to:
  - Decrease cytoplasmic Ca$^{2+}$ levels and increase intramuscular and cerebral phosphocreatine stores
  - Attenuate effects of sarcopenia
  - Facilitate rehabilitation after disuse atrophy

Treatment - Supplements

– Creatine monohydrate
  • No short- or long-term side effects from “recc’ d doses” in studies
  • Cochrane database: evidence from randomized trials does not show significant improvement in muscle strength in metabolic myopathies
    – BUT only 33 participants in 12 RCTs
  • Reported doses in trials
    – 3 gm/d to 20 gm/d, anywhere from 4 weeks to 6 months

– Others
  • Antioxidants (Vit C, E, alpha lipoic acid)
  • Electron donors (Idebenone, thiamine, riboflavin, biotin)
  • Reduce lactic acid (dichloroacetate, nicotinamide, Vit K3, l-arginine)

Kley RA et al: Cochrane Database of Systemic Reviews, 2007
Treatment - Supplements

Others (adult doses based on Rx for MELAS **)

Antioxidants
• Alpha-lipoic acid 200-600 mg/d in 3 divided doses
• Vit C 250-4000 mg/d po in 1-3 divided doses
• Vit E 400-1200 IU/d in 1-3 divided doses

Electron donors
• Idebenone 90-270 mg po qd
• Riboflavin 50-400 mg po qd
• Thiamine 50-300 mg po qd

Drugs to reduce lactic acid
• Dichloroacetate 25-50 mg/kg/d po in 2 divided doses
• L-arginine: 150-300 mg/kg/d po in 2-3 divided doses
• Nicotinamide 50-500 mg po qd
• Vit K3 40-80 mg po qd

Treatment – Enzyme Replacement

**Acid maltase deficiency (GSD II)**

- mutations in the gene for acid α-glucosidase (GAA)
  - nonsense mutations (infantile form)
  - missense and splicing mutations in later onset disease

- **recombinant human GAA (rhGAA)**
  - first pilot trial Feb 1999 in 4 children; approved 2006
  - first placebo-controlled trial (mainly adults) published 2010
    - improved distance on 6 min walk, and FVC %predicted
  - immune reaction in infants with null mutations and no GAA protein
  - assumption into lysosomes probably hindered by lysosomal engorgement with glycogen

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Objectives

• Discuss the *sources of energy* for muscle metabolism.

• Describe a systematic diagnostic approach to the patient presenting with a suspected metabolic myopathy, *correlating defects in energy production pathways with symptoms and laboratory studies*.

• **Summarize available therapies** for patients with metabolic myopathies.
Fig. 1 Clinical algorithm for patients with exercise intolerance in whom a metabolic myopathy is suspected. CK—creatinine kinase; COX—cytochrome c oxidase; CPT—carnitine palmitoyl transferase; cyt b—cytochrome b; mtDNA—mitochondrial DNA; nDNA—nuclear DNA; PFK—phosphofructokinase; PGAM—phosphoglycerate mutase; PGK—phosphoglycerate kinase; PPL—myophosphorylase; RRF—ragged red fibers; TFP—trifunctional protein deficiency; VLCAD—very long-chain acyl—coenzyme A dehydrogenase
Selected References


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