Metabolic Myopathies

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**Metabolic Myopathies** - decreased muscle energy supply due to biochemical abnormalities.

Carbohydrates are essential for *anaerobic* energy needs (primarily – **cytoplasmic glycogen** → glycogenolysis → glycolysis).

Lipids are essential for *aerobic* energy needs during sustained exercise (primarily - **serum long-chain fatty acids** → β-oxidation in mitochondria).

1. **dynamic (exercise-induced) myopathies** - symptoms (acute myalgias, stiffness → contractures, intermittent weakness → myoglobinuria\*) appear during / after exercise:

\* drink fluids after exercise!

* 1. **carbohydrate metabolism disorders** - type V (most common), type VII-XI glycogenoses, Satoyoshi disease; [see p. 734-738 >>](http://www.neurosurgeryresident.net/USMLE%202\Biochemistry,%20Metabolic%20Disorders%20(501-900)\734.jpg)
* *hemolytic anemia* accompanies only type VII (mild) and type IX (severe).
  1. **lipid metabolism disorders** - carnitine palmitoyl transferase deficiencies

[see p. 750 >>](http://www.neurosurgeryresident.net/USMLE%202\Biochemistry,%20Metabolic%20Disorders%20(501-900)\750.%20Fatty%20Acid%20Oxidation%20Disorders.pdf)

* 1. **purine metabolism disorders** - myoadenylate deaminase deficiency [*see below* >>](#MYOADENYLATE_DEAMINASE_DEFICIENCY)
  2. **mitochondrial myopathies** - succinate dehydrogenase deficiency
* *exercise intolerance* in childhood;

*exertion-induced symptoms* (muscle pain, weakness, myoglobinuria) in 2-3rd decade.

* + - ***contractures*** cause intense muscle pain, are electrically silent and not associated with ATP depletion.
    - exercise tolerance can be enhanced by slow induction phase (warm-up) or brief rest periods allowing for start of *"second-wind" phenomenon* (i.e. patient can continue exercise at previous level of activity after brief rest - switching to utilization of fatty acids).
* between attacks, muscle strength, diagnostic test results are normal (may become abnormal with advancing age).

1. **static (stable or slowly progressive) myopathies** - chronic fixed progressive weakness (simulates muscular dystrophy; no exercise intolerance, no myoglobinuria):
   1. **carbohydrate metabolism disorders** - type II-IV glycogenoses. [see p. 734-738 >>](http://www.neurosurgeryresident.net/USMLE%202\Biochemistry,%20Metabolic%20Disorders%20(501-900)\734.jpg)
   2. **lipid metabolism disorders** - carnitine deficiencies: [see p. 750 >>](http://www.neurosurgeryresident.net/USMLE%202\Biochemistry,%20Metabolic%20Disorders%20(501-900)\750.%20Fatty%20Acid%20Oxidation%20Disorders.pdf)
      1. primary (muscle / systemic)
      2. secondary (β-oxidation defects, valproic acid)
   3. **mitochondrial myopathies** (most)

N.B. type I and VI glycogenoses do not affect muscles!

Diagnosis

1. **Forearm (grip) exercise** - information about glycolytic (anaerobic) metabolism by evaluating *lactate* production in **ischemic exercise**:

* rested, rested and fasting patient ***repetitively squeezes handheld ergometer*** while BP cuff is maintained above systolic pressure (induced ischemia prevents oxidative phosphorylation).
  1. workload 4-7 kg-m at 60 Hz for 1 min (such duration does not induce ischemic pain).
  2. sustain 1.5-second contractions separated by 0.5-second rest periods for 1 minute.
  3. squeeze to 50% of maximum grip strength until exhaustion (usually ≈ 10 minutes).
* **nonischemic workload** > 6-7 kg-m (well exceeds aerobic threshold) also produces comparable results and *avoids induced ischemia* (may cause severe muscle necrosis in glycolytic defects).
* venous [lactate] and [ammonia] are determined from antecubital vein proximal to deep veins of forearm (e.g. median vein):
* pre-exercise;
* postexercise (1, 2, 4, 6, 10 minutes).
* ***normally***: [lactate] rises 3-5-fold within 1-2 minutes after exercise;

[ammonia] rises 2-10-fold within 2-5 minutes after exercise.

*glycogenosis* – [lactate] elevation does not occur (or is diminished); muscle develops painful contracture;

*lipid metabolism disorders* – normal profile;

*myoadenylate deaminase deficiency* – [ammonia] elevation does not occur;

*mitochondrial disorders* – excessive [lactate] elevation;

*poor effort* – neither [lactate] nor [ammonia] increase.

1. **Incremental bicycle ergometry** - information about aerobic metabolism.
2. **31P** **MR spectroscopy** - information about intracellular energy metabolites (i.e. ATP, inorganic phosphate, phosphocreatine).
3. **EMG**:
4. dynamic myopathies:
   * + *during episode* - electrical silence.
     + *after episodes* of severe myoglobinuria - myopathy and fibrillations.
     + *between episodes* – normal.
5. static myopathies – myopathy, excessive irritability (incl. myotonic discharges, particularly in lumbosacral paraspinous muscles in Pompe disease).
6. **Muscle biopsy**:
   1. scattered ***necrotic & regenerating fibers*** (esp. after rhabdomyolysis episode).
   2. ***specific findings*** (e.g. vacuolar glycogen or lipid accumulations).
   3. specific ***enzyme deficiency*** (alternatively skin fibroblasts, intestinal mucosa, lymphocytes may be examined) – definitive diagnosis!
7. **Serum CK** moderately increased (very increased after attacks\* and usually normal between attacks of dynamic myopathies).

\*together with myoglobinuria

1. **Genetic analysis for mutations**

Myoadenylate Deaminase Deficiency

**Myoadenylate deaminase (s. muscle AMP deaminase)** provides short-term ATP supply by catalyzing conversion of AMP → IMP through removal of ammonia. [see p. 832 >>](http://www.neurosurgeryresident.net/USMLE%202\Biochemistry,%20Metabolic%20Disorders%20(501-900)\832.jpg)

1. exertional myalgia ± myoglobinuria (**dynamic myopathy**)
2. **asymptomatic** (myoadenylate deaminase gene 1p13-21 is mutated in ≈ 2% normal people).

* ***forearm exercise test*** - no increase in [ammonia].

Bibliography for ch. “Metabolic Disorders” → follow this [link >>](http://www.neurosurgeryresident.net/Mus.%20Muscular,%20Neuromuscular%20disorders\Mus.%20Bibliography.pdf)

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