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!
   A) **carbohydrate metabolism disorders** - type V (most common), type VII-XI glycogenoses, Satoyoshi disease; see p. 734-738 >>
      – *hemolytic anemia* accompanies only type VII (mild) and type IX (severe).
   B) **lipid metabolism disorders** - carnitine palmitoyl transferase deficiencies see p. 750 >>
   C) **purine metabolism disorders** - myoadenylate deaminase deficiency *see below* >>
   D) **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).

2. **STATIC (stable or slowly progressive) myopathies** - chronic fixed progressive weakness (simulates muscular dystrophy; no exercise intolerance, no myoglobinuria):
   A) **carbohydrate metabolism disorders** - type II-IV glycogenoses. see p. 734-738 >>
   B) **lipid metabolism disorders** - carnitine deficiencies: see p. 750 >>
      1) primary (muscle / systemic)
      2) secondary (β-oxidation defects, valproic acid)
   C) **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).
     a) workload 4-7 kg-m at 60 Hz for 1 min (such duration does not induce ischemic pain).
     b) sustain 1.5-second contractions separated by 0.5-second rest periods for 1 minute.
     c) 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.

2. **Incremental bicycle ergometry** - information about aerobic metabolism.

3. **^{31}P MR spectroscopy** - information about intracellular energy metabolites (i.e. ATP, inorganic phosphate, phosphocreatine).

4. **EMG**:
   A) DYNAMIC myopathies:
      – *during episode* - electrical silence.
      – *after episodes* of severe myoglobinuria - myopathy and fibrillations.
      – *between episodes* – normal.
   B) STATIC myopathies – myopathy, excessive irritability (incl. myotonic discharges, particularly in lumbosacral paraspinous muscles in Pompe disease).

5. **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!

6. **Serum CK** moderately increased (very increased after attacks* and usually normal between attacks of DYNAMIC myopathies).
   *together with myoglobinuria

7. **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 >>

a) exertional myalgia ± myoglobinuria (**DYNAMIC myopathy**)
b) **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 >>