Skeletal Muscle CHANNELOPATHIES

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CHANNELOPATHIES: disorders of ion channels that result in altered excitability of cellular membranes. In case of skeletal muscle channelopathies:

a) hyperexcitability → myotonia
b) hypoxic excitability → periodic paralysis.

• acquired (usually autoimmune) channelopathies also exist (e.g. neumyotonia).

SODIUM CHANNEL α-subunit (17q23-25):

Hyperkalemic periodic paralys:
with myotonia
without myotonia
with paramyotonia congenita

Paramyotonia congenita
Sodium channel myotoni:
Myotonia fluctuans
Myotonia permanens
Acetazolamide-responsive myotonia

CHLORIDE channel (7q32):
Autosomal dominant myotonia congenita (Thomsen)
Autosomal recessive myotonia congenita (Becker)

CALCIUM channel α1 subunit (6q13-32):

Hypokalemic periodic paralys∗

Figure 16-11: The myotonia and periodic paralyses are caused by mutations in genes for diverse voltage-gated ion channels, the channels disorders are characterized by myotonia, some only by periodic paralys, and some by myotonia and paralys. Some clinical disorders (e.g. hypokalemic periodic paralysy) may arise from defects in different channels in different individuals.

*most frequent form of periodic paralysy*

MYOTONIAS:

Myotonia – impaired muscle relaxation after forceful voluntary contraction (painless muscle stiffness); specific EMG pattern; with repeated exercise, myotonia improves (“warm-up phenomenon”).

Pseudomyotonia (G. PARATOMYONIA) – impaired relaxation without electrical evidence of myotonia; exercise makes pseudomyotonia worse.

Exposure to cold worsens both myotonia and paramyotonia!

A. DYSTROPHIC MYOTONIAS (considered MYODYSTROPHIES not channelopathies) – myotonia is one of several muscle symptoms, with muscle atrophy & weakness being most prominent: see p. Mus5 >>

1. Myotonic dystrophy (s. Steinert disease)
2. Proximal myotonic dystrophy (s. Thronborg-Griggs-Moxley disease)

B. NONDYSTROPHIC MYOTONIAS – myotonia is most prominent symptom, see p. Mus5 >>

Diagnosis

Serum CK – normal (elevated 2-5 times in Thomsen’s & Becker’s diseases).

EMG – spontaneous myotonic discharges. see p. D20 >>

1. in paramyotonia congenita, provocation by cooling is required.

EMG also shows decrement in compound motor action potential (CMAP) with exercise or with high-frequency 30-Hz stimulation (esp. in Becker’s disease - CMAP decrement causes transient weakness).

1. in Schwartz-Jampel syndrome, EMG shows continuous spontaneous motor activity with few of fluctuations in frequency and amplitude.

N.B. myotonia persists after curarization!

Muscle biopsy – (rare abnormalities) (may be variations in fiber size with fiber hypertrophy and increased central nuclei).
Differential diagnosis
1) pseudomyotonia
2) spasticity / rigidity (motor neurone disorders)
3) muscle cramps (peripheral nerve disorders).
4) dystonia (extrapyramidal discharges of whole motor units rather than individual muscle fibers) → abnormal postures.
5) contractures (metabolic myopathy such as McArdle's disease) - painless electrically silent.
6) neurologic malignant syndrome.
7) tetanus.\n
Management
Myotonia congenita
N.B. myotonia can be exacerbated by:
1) severe muscle relaxants & anticholinesterases (anesthesia should be planned accordingly).
2) potassium supplements.
3) treatment of (myotonia congenita) relies on membrane-stabilizing drugs:
   a) PRIMIDONE - for chronic administration.
   b) PROCAINAMIDE - used intermittently (likely to produce cardiac side effects).
4) occasionally myotonia is responsive to ACETAZOLAMIDE, MEXILETINE

PERIODIC PARALYSES

Inherited classification:
A. Associated with high / normal serum [K+] (i.e. hyperkalemic periodic paralysis)
B. Associated with low serum [K+] (i.e. hypokalemic periodic paralysis).

Diagnosis
1) serial blood tests (during weakness episode) for K+, Ca++, Mg++, phosphate, CK.
   - each time blood sample is taken, muscle strength is tested.
   - K+ levels are checked every 15-30 min to determine direction of change when muscle strength is decreasing or improving.
N.B. K+ level may be normal during hyperkalemic periodic paralysis and occasionally in hypokalemic periodic paralysis.

2) ECG - hypokalemia / hyperkalemia.
   - if fixed weakness has developed, EMG shows myopathic changes.
   - even if initial EMG is normal, there may be exaggerated increment followed by decline in CMAP with high-frequency 30-Hz stimulation.
3) nerve conduction studies – normal (exclude neurogenic causes); muscles do not respond to electrical stimulation during attack.

5) muscle biopsy: – hypokalemic periodic paralysis – pathognomonic large central vacuoles, occasional necrotic fibers.
   - vacuoles (dilations of sarcoplasmic reticulum terminal cisterns) are PAS-positive, intermyofibrillar, especially evident during episodes of acute weakness.

6) provocative testing to produce weakness (under careful supervision):
   a) hypokalemic challenge – iv 100 g glucose + 20U regular insulin (to drive K+ into cells).
   b) hyperkalemic challenge – repeated doses of oral KCl (contraindicated in renal disease and diabetes).

Differential Diagnosis

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<tr>
<th>Disorder</th>
<th>Key Features</th>
<th>Diagnostic Tests</th>
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</thead>
<tbody>
<tr>
<td>Hyperkalemic</td>
<td>More frequent; provoked by test after exercise</td>
<td>KCl load</td>
</tr>
<tr>
<td>Normokalemic</td>
<td>More severe and prolonged than hyperkalemic</td>
<td>KCl load</td>
</tr>
<tr>
<td>Hypokalemic</td>
<td>Nocturnal, lasts hours to days</td>
<td>Carbohydrate load after exercise</td>
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</tbody>
</table>

N.B. hyperkalemic periodic paralysis may have coexistent myotonia!

Other causes of flaccid, areflexic tetraparesis without sensory signs:
1) metabolic – Ca++; phosphate, Mg+++, rhabdomyolysis.
2) neurologic – Guillain-Barre syndrome, myasthenic syndrome, acute polynymyelitis.
3) secondary hypokalemic periodic paralysis (results from intracellular K+ depletion) usually late onset with marked hypokalemia (vs. primary form – rarely starts after age 30; serum [K+] may be normal)
   a) renal - jugulomastoidal hyperplasia (Bartter syndrome), renal tubular acidosis, Fanconi syndrome.
   b) endocrine - primary hyperaldosteronism (Conn syndrome), thyrotoxic periodic paralysis (see below).
   c) gastrointestinal – fistula, laxative abuse, villous adenoma, pancreatic noninsulin-secreting tumors with diarrhea, nonspecific cause.
   d) drug-induced: amphotericin B, licorice, carbonostone, corticosteroids, paminosalicylic acid, K-depleting diuretics.

Management
Hyperkalemic periodic paralysis (attacks should be treated to prevent permanent weakness!)

- attack termination – glucose + insulin iv calcium gluconate
- attack prophylaxis:
  a) urinary K+ excretion promoters - ACETAZOLAMIDE, alternatives - thiazides, FLUIDURET/BYSTINE.
b) Na/K-ATPase activators - inhibited β-adrenergics (e.g. SALBUTAMOL).
c) high-carbohydrate low-potassium diets.
d) avoid fasting, strenuous activity, cold.

Hypokalemic periodic paralysis

- attack precipitated by - ACETAZOLAMIDE up to 1.5-2.0 g/d (or oral KCl), low-carbohydrate & low-sodium diet.

N.B. prophylactic potassium alone (even in large doses) does not prevent attacks!
- mechanism of action of acetzolamide is uncertain (beneficial effect may be related to mild metabolic acidosis it induces).
- if acetzolamide does not prevent attacks (~10% patients), try TRIAMTERENE or SPIRONOLACTONE.

- attack termination – KCl 0.2-0.4 mmol/kg in unsweetened oral solution q15-30 min + ECG ≠ β-blockers.
- if parenteral administration is necessary (repeated KCl IV boluses 0.1 mmol/kg), use MANIPOT as vehicle (if 5% glucose or saline is used, serum potassium may decline, and weakness may worsen!).

N.B. there is some phenotypic overlap among sodium channelopathies – they are part of continuum rather than distinctly categorized clinical entities.
- all begin in 1st decade and continue throughout life.

Hypokalemic periodic paralysis

- frequent attacks of paresis;
  - precipitated by K ingestion (!!!) or cold or rest following exercise or fasting;
  - occur in daylight, 2-3 wkd (commonly before breakfast);
  - brief (15 min or 4 hrs) and mild;
  - weakness is mainly proximal (distal muscles can be involved); no ocular or respiratory weakness;
  - often paresthesia and muscle pain.

severe attack = flaccid tetraparesis + absent reflexes + normal sensory examination.

- [K] usually rises during attack (K leakage from muscle = excessive Na influx is accompanied by excessive K efflux);
  - not necessarily above upper normal;
  - rarely to levels that cause cardiac dysrhythmias;
  - normokalemia does not preclude diagnosis! (so better term is POTASSIUM-SENSITIVE PERIODIC PARALYSIS)

- between attacks, most patients maintain normal strength (few have persistent mild limb-girdle weakness).
- attack frequency declines as patient grows older.
- in some families – mild coexisting sodium channelopathy.
- in few families - arhythmia and sudden death in young children.

Myotonias

- MYOTONIA PERMANENS
- MYOTONIA FLUCTUANS
- D...myotonia).
- weakness is rarely serious enough to require acute therapy.

Hyperkalemic periodic paralysis

- inherited mutations in [17q23]
- subunit of voltage-dependent Na+ channel gene (SNC4A) → reduced inactivation of Na+ channel* → increased muscle:
  a) inexcitability → HYPERKALEMIC PERIODIC PARALYSIS (exacerbated by extracellular K+).
  b) excitability → SODIUM CHANNEL MYOTONIAS; PARAMYOTONIA CONGENITA (exacerbated by cooling).
- *muscle is partially depolarized at rest (this can be blocked by tetrodotoxin - specifically affects α-subunit of Na channel)
- autosomal dominant inheritance with almost complete penetrance.

N.B. there is some phenotypic overlap among sodium channelopathies – they are part of continuum rather than distinctly categorized clinical entities.
- all begin in 1st decade and continue throughout life.

SODIUM CHANNEL MYOTONIAS

- group of channelopathies not characterized by periodic paralysis or paramyotonia phenotypes.

ACETAZOLAMIDE-RESPONSIVE MYOTONIA - myotonia becomes worse with cold, but it is not associated with weakness and responds to ACETAZOLAMIDE.

MYOTONIA FLUCTUANS - myotonia fluctuates on daily basis, provoked by exercise.

MYOTONIA PERMANENS - permanent very severe myotonia.
**Diagnosis, Differential Diagnosis, Management**

--- see above ---

**Cl⁻ channelopathies**

**Genetics & Pathophysiology**
- allele-specific mutations in \( \text{CACNL1A3} \) → reduced membrane Cl⁻ conductance → membrane hyperexcitability with after-depolarization and repetitive firing → myotonia.

**Clinical Features**
- two similar forms with different inheritance - autosomal dominant (Thomsen's disease) and autosomal recessive (Becker's disease).

**Autosomal Dominant MYOTONIA CONGENITA (THOMSEN disease)**

- incidence: 0.25-4.0 per 100,000.
- appears in 1-2nd decades of life.
- painless generalized myotonia (perceived as muscle stiffness).
  - myotonia is more severe than in myasthenic dystrophy - myotonia may be functional handicap!
  - provoked by exertion following rest (e.g. ask patient to rise from chair after period of quiet sitting; percussion-induced myotonia can also be demonstrated).
  - cold increases myotonia.
  - warm-up phenomenon - myotonia improves with exercise → well-developed muscles (esp. hypertrophy of legs and buttocks, with some hyperlordosis) → athletic appearance, muscle strength may be stronger than normal (advantage in power sports in which speed is not requisite).
  - respiratory is spared.
  - normal reflexes.
  - no involvement of heart or other organs.
  - clinically stable and not progressive for many years - patients adapt well and live normal life span.

**Autosomal Recessive MYOTONIA CONGENITA (BECKER disease)**

- Thomsen disease (myotonia, muscle hypertrophy, etc); differences:
  - myotonia appears later in first decade.
  - myotonia can be more severe.
  - patients may have disabling transient weakness (not seen in Thomsen's disease!)
    - muscles are initially weak, and period of activity is required before full strength returns.
    - weakness may be so severe that patient requires assistance with ambulation.
    - persistent weakness may occur.

--- see above ---

**Ca²⁺ channelopathies**

**Hypokalemic Periodic Paralysis**

**Genetics & Pathophysiology**
- mutations in \( \text{CLCNK} \) → o-subunit of voltage-sensitive Ca²⁺ channel (\( \text{CACNL1A3, CACNL1B} \)).
  - primary role in electrocontraction coupling

**Unknown mechanism causes increased sensitivity to insulin → K⁺ movement into muscle cells (independently of glucopenic action) → muscle fibers become depolarized and excitable (vs. normal fibers) → hypokalemic paralysis (e.g. after large carbohydrate meals).

N.B. weakness is severe at serum [K⁺] levels that do not affect normal individuals.
- autosomal dominant inheritance.
- more common in males (because of reduced penetrance in females).

**Clinical Features**
- incidence: 0.4-1.25 per 100,000.
- Attacks begin later, are longer, less frequent, and more severe than in hyperkalemic paralysis
  - onset in adolescence (invariably < 30 yrs).
  - attacks precipitated by carbohydrate intake (glucose, alcohol intake, rest after exercise, emotional stress (effect of epinephrine)); no sensitivity to cold.
  - attacks often occur at night or morning (patient awakens with weakness).
  - carbohydrate breakfast day after vigorous exercise.
  - prodromal symptoms (muscle stiffness, heavy limbs, swelling) → proximal lower limb weakness → flaccid areflexic tetraplegia
    - if patient performs mild exercise full-blown attack may be aborted (“waking it off!”)
    - ocular / bulbar involvement is rare; muscles that remain active in sleep (respiratory, cardiac muscle) are not affected.
    - oliguria during attack (water sequestration intracellularly together with K⁺); K⁺ content of urine is decreased.
    - attacks last 1-12 hours (occasionally up to 3 days).
    - fatalities are rare (e.g. hypokalemic-induced dysrhythmias, respiratory paralysis).
    - attack frequency (less than in hyperkalemic periodic paralysis) varies from daily to only once in lifetime; frequency decreases with age (may cease altogether after age 40-50).
    - interictal abnormalities:
      * younger subjects - normal strength, eyelid myotonia (in 50%)
      * older subjects - persistent weakness (attributed to vacuolar myopathy).

--- see above ---

**Diagnosis, Differential Diagnosis, Management**

--- see above ---
Other / Possible Channelopathies

SCHWARTZ-JAMPLE syndrome (s. chondrodysplastic myotonia)
- rare autosomal recessive (1p34.1-36.1) myotonic disorder of unknown etiology (disorder of ATPase)
- onset - before age 3 yrs.
- severe continuous motor activity and muscle stiffness, particularly in face and thighs.
  - masklike face (recognizable at birth) with blepharophimosis, pinched nose, micrognathia, and continuous motor activity of chin and lips.
  - muscle (esp. thigh) hypertrophy.
- dystrophy of epiphyseal cartilages → variety of skeletal malformations (flexion contractures, dwarfism, kyphosis, etc) - cause most disability!
- EMG - continuous myotonia with little wakening and waning (i.e. continuous high-frequency electrical activity).

THYROTOXIC PERIODIC PARALYSIS
- clinically often indistinguishable from hypokalemic periodic paralysis but with additional, sometimes subtle, hyperthyroism.
- N.B. paralysis and hypokalema may be profound, with fatalities reported!
- results from alteration in muscle membrane permeability (decreased activity of Ca2+ pump?).
- most common in young Latin American and Asian males (among them, up to 10% thyrotoxic patients may have this condition!).
- treatment of thyrotoxicosis abolishes attacks! - β-blockers reduce attacks while thyrotoxicos
- acute attacks respond to KCl.

ANDERSEN’S SYNDROME
- rare autosomal dominant disorder with:
  1) PERIODIC PARALYSIS (hypo-, hyper-, or normo-kalemic) - begins insidiously in children ÷ young adults.
  2) periodic paralysis → channel inactivation → localized transient muscle swelling or rippling.
  3) prolonged QT interval, life-threatening ventricular arrhythmias.

BROYDE’S DISEASE
- mutations in 16p12.1 sarcolemmal reticulum Ca2+-ATPase gene (esp. in type 2 muscle fibers).
- extrudes Ca2+ out of cytoplasm into sarcoplasmic reticulum.
- genetic heterogeneity - autosomal dominant, autosomal or X-linked recessive inheritance.
- only about 21 cases have been recorded in literature.

NEUROMYOTONIA (skeletal myotonia)
- begins in childhood - exercise-induced myotonia (i.e. pseudomyotonya)
  - eyelid and grip but not percussion myotonia!
  - initially affects limbs, later face and trunk.
- slowly progressive or stationary.
- mild muscle atrophy and weakness in final stages.

TREATMENT - DANTROLENE, Ca-channel blockers.

RIPPLING MUSCLE DISEASE
- autosomal dominant mutations in 1p34.1 localized transient muscle swelling or rippling induced by percussion or exercise (patient complain of tightness in thighs or upper arms).

NEUROMYOTONIA (s. ISAACS’ syndrome)
- acquired channelopathy - autoantibodies against voltage-gated K+ channels on peripheral nerves → channel inactivation → MYOTONIC MOTOR NERVE → continuous muscle fiber activity (paresthesias even during sleep).
- continuous discharges may originate anywhere along length of peripheral nerve (abolished by curare but usually persists after general anesthesia).

PRINCIPLES - autonomic
- sometimes associated with tumor (paraneoplastic syndrome), e.g. thymoma, small cell lung carcinoma, lymphoma.
- autonomic dominant form exists - EPISODIC ATAXIA TYPE I - defect in K+ channel seen p. Mov50

PRINCIPAL FEATURES - begins insidiously in children ÷ young adults.
- progresses slowly for months or few years.
- symptoms are seen at rest and persist in sleep.

1. MYOKYMIA - continuous vigorous fasciculation* → specific EMG.
2. Persistent or intermittent ABNORMAL DYSTAL** LIMP POSTURES (identical to carpal or pedal spasm - finger clawing, toe-walking);
- *vs. stiff-person syndrome - proximal & axial muscles are affected most severely

**results in occasional muscle hyperreflexia

*continuous muscular fasciculation

**abnormal distal limb postures
Skeletal Muscle Channelopathies

1. Late stiffness of proximal & axial muscles;
   - occasionally, oropharyngo-laryngeal or respiratory muscles are affected.
2. Stiffness (pseudomyotonia) - clinically resembles true myotonia (voluntary contraction induces spasm that persists during attempted relaxation); no percussion myotonia.
3. Liability to CRAMPS with HYPERHYDRIDOSIS.

DIAGNOSIS

1) EMG (recorded from stiff muscles) - continuous prolonged, irregular discharges (action potentials vary in amplitude and configuration; some of them resemble fibrillations) and 150-300 Hz bursts;
   - EMG is positive even in absence of visible myokymia.
   - voluntary effort triggers more intense discharges that persist during relaxation (interferes with clinical relaxation).
2) nerve conduction may be slow.
3) sural nerve biopsy may be abnormal.
4) CK can be mildly elevated.
5) CSF - elevated protein and oligoclonal bands.
6) specific antibodies in serum.

TREATMENT

1) PHENYTOIN, CARBAMAZEPINE.
2) immunosuppressive agents, plasmapheresis.

BIBLIOGRAPHY for ch. “Neuromuscular, Muscular Disorders” → follow this LINK >>

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