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) hypoexcitability → **periodic paralysis**.

- **acquired** (usually *autoimmune*) channelopathies also exist (e.g. neuromyotonia).

SODIUM channel α-subunit (17q23-25)
Hyperkalemic periodic paralysis:
with myotonia
without myotonia
with paramyotonia congenita
Paramyotonia congenita
Sodium channel myotonias:
Myotonia fluctuans
Myotonia permanens
Acetazolamide-responsive myotonia
CHLORIDE channel (7q32)
Autosomal dominant myotonia congenita (Thomsen)
Autosomal recessive myotonia congenita (Becker)
CALCIUM channel α-1 subunit (lq31-32)
Hypokalemic periodic paralysis*

*most frequent form of periodic paralysis!

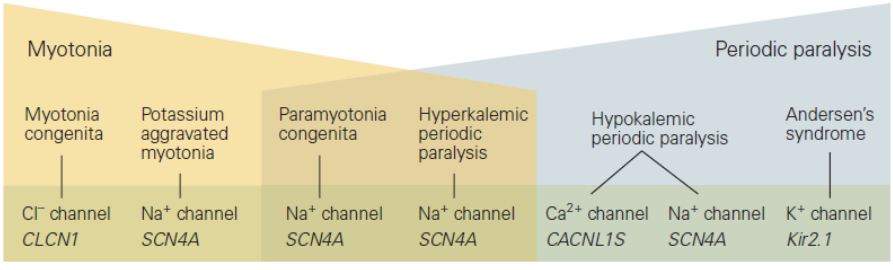

Figure 14–13 The myotonias and periodic paralyses are caused by mutations in genes for diverse voltage-gated ion channels in the skeletal muscle membrane. Some channel disorders are characterized only by myotonia, some only by periodic paralysis, and some by myotonia and paralysis. Some clinical disorders (eg, hypokalemic periodic paralysis) may arise from defects in different channels in different individuals.

MYOTONIAS

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

PSEUDOMYOTONIA (S. PARAMYOTONIA) – 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. Thornton-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 >>

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

N.B. myotonias persists after curarization!

Muscle biopsy - few abnormalities (may be variations in fiber size with fiber hypertrophy and increased central nuclei).

- in ***hyperkalemic periodic paralysis with paramyotonia congenita***, vacuolated and necrotic fibers may occur.
- in ***myotonia congenita***, may be lack of 2B fibers.
- in ***Schwartz-Jampel syndrome***, various degrees of nonspecific myopathic features; dilated sarcotubular system.

Differential diagnosis

1) **pseudomyotonia** (acid maltase deficiency, Brody's disease).
2) **spasticity / rigidity** (motoneuron 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) **neuroleptic malignant syndrome**.
7) **tetanus**, **tetany**

Management

Myotonia congenita

N.B. myotonia can be exacerbated by:

1) several muscle relaxants & anticholinesterases (anesthesia should be planned accordingly).
2) potassium supplements.

- treatment (of myotonia congenita) relies on **membrane-stabilizing drugs**:
  1) PHENYTOIN - for *chronic* administration.
  2) PROCAINAMIDE, QUININE - used *intermittently* (likely to produce cardiac side effects).
- occasionally myotonia is responsive to ACETAZOLAMIDE, MEXILETINE

Paramyotonia congenita

- attack termination – IV **calcium gluconate** + **glucose** + **insulin**.
- attack prophylaxis:
  - **thiazides**.
  - **Na-channel blocker** MEXILETINE (useful for both myotonia and associated weakness).

PERIODIC PARALYSES

Historic* classification:

A. Associated with **high / normal serum [K^+]** (i.e. hyperkalemic periodic paralysis)

B. Associated with **low serum [K^+]** (i.e. hypokalemic periodic paralysis).

*abnormal serum [K^+] is clearly consequence rather than cause of periodic paralysis!

Diagnosis

1) **serial blood tests** (during weakness episode) for K^+, Ca^{2+}, Mg^{2+}, 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***.

   N.B. between attacks of periodic paralysis, serum [K+] is normal (vs. secondary hyperkalemic / hypokalemic forms)!
2) **ECG** - hypokalemia / hyperkalemia.
3) **EMG** - reduced CMAP (proportionate to degree of weakness);
   - 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.
4) **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.
   - ***hyperkalemic periodic paralysis*** - smaller **VACUOLES**, **TUBULAR AGGREGATES**. see p. D30 >>
6) **provocative testing** to produce weakness (under careful supervision):
   a) ***hypokalemic challenge*** – i/v 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

Disorder	Key Features	Diagnostic Tests
Hyperkalemic	More frequent; provoked by rest after exercise	KCI load
Normokalemic	More severe and prolonged than hyperkalemic	KCI load
Hypokalemic	Nocturnal, lasts hours to days	Carbohydrate load after exercise

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

1) other causes of **flaccid, areflexic tetraparesis without sensory signs**:
   a) **metabolic** – Ca^{2+}↓↑, phosphate↓, Mg^{2+}↓, rhabdomyolysis.
   b) **neurologic** – Guillain-Barré syndrome, myasthenic syndrome, acute poliomyelitis.
2) **SECONDARY HYPOKALEMIC 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** - juxtaglomerular 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, nontropical sprue.
   d) **drug-induced**: amphotericin B, licorice, carbenoxolone, corticosteroids, p-aminosalicylic acid, K-depleting diuretics.

Management

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

- attack termination – **glucose** + **insulin** ± i/v **calcium gluconate**
- attack prophylaxis:
  a) **urinary K^+ excretion promoters** - ACETAZOLAMIDE; alternatives - **thiazides**, FLUDROCORTISONE.

b) **Na/K-ATPase activators** - **inhaled β-adrenergics** (e.g. SALBUTAMOL).
c) *high-carbohydrate* / *low-potassium* diets.
d) avoid fasting, strenuous activity, cold.

Hypokalemic periodic paralysis

- attack prophylaxis - ACETAZOLAMIDE up to 1,5-2,0 g/d (± oral KCl), *low-carbohydrate & low-sodium* diet.
  N.B. prophylactic potassium alone (even in large doses) does not prevent attacks!
  – mechanism of action of acetazolamide is uncertain (beneficial effect may be related to mild metabolic acidosis it induces).
  – if acetazolamide 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 i/v boluses 0.1 mmol/kg), use MANNITOL as vehicle (if 5% GLUCOSE or SALINE is used, serum potassium may decline, and weakness may worsen!).

Na^+ channelopathies

GENETICS & PATHOPHYSIOLOGY

- allelic point mutations in 17q23-25 - **α-subunit** of **voltage-dependent Na^+ channel gene** (SCNA4A) → **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.

CLINICAL FEATURES

N.B. there is *some phenotypic overlap* among sodium channelopathies – they are part of continuum rather than rigidly demarcated clinical entities.

- all begin in 1st decade and continue throughout life.

HYPERKALEMIC PERIODIC PARALYSIS

- frequent attacks of paresis:
  – precipitated by *K ingestion* (!!!) or *cold* or *rest following exercise* or *fasting*.
  – occur in DAYTIME - 2-3 ×/d (commonly ***before breakfast***).
  – brief (15 min ÷ 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 **(para)myotonia** (most often in eyelids) – demonstrable by EMG, but rarely clinically (cooling may provoke weakness but not myotonia!).
- in few families - **arrhythmia** and **sudden death** in young children.

DIAGNOSIS, DIFFERENTIAL DIAGNOSIS, MANAGEMENT – *see above >>*
Weakness is rarely serious enough to require acute therapy.

PARAMYOTONIA CONGENITA (s. EULENBURG disease)

- **paradoxical myotonia (s. pseudomyotonia)** - increases with ***repetitive movements**** (unlike classic myotonia).

* best observed on repeated forced eye closure: after several attempts patient cannot open eyelids.

- present from birth and persists throughout life (nonprogressive).
- particularly affects *face*, *neck*, and *forearms*.
- exacerbated by ***cold*** (which also causes weakness!).

walking in cold weather

  – in warm environment, patients may have no symptoms at all.
  – spontaneous attack rate < 1/month.
- typically, *on relief of myotonia* (either spontaneously or with muscle warming), variable degree of **weakness** occurs (can persist for several hours).
  – in some families, attacks of paralysis occur *independently of myotonia* (in many, these attacks are precipitated by *K ingestion*).
- no muscle atrophy or hypertrophy.

DIAGNOSIS, DIFFERENTIAL DIAGNOSIS, MANAGEMENT – *see above >>*

SODIUM CHANNEL MYOTONIAS

- group of ***K-sensitive*** disorders 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

- allelic point mutations in 7q35 – **Cl^- channel gene** (CLC9I) → **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 myotonic 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).
- respiration 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.

DIAGNOSIS, DIFFERENTIAL DIAGNOSIS, MANAGEMENT – *see above >>*

Ca^{2+} channelopathies

HYPOKALEMIC PERIODIC PARALYSIS

GENETICS & PATHOPHYSIOLOGY

- mutations in 1q31-32 - **α-1 subunit** of **voltage-sensitive Ca^{2+} channel** (CACNL1A3, s. dihydropyridine receptor)*.

* 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 *inexcitable* (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*** (!!!) / ***sodium*** / ***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, sweating)* → proximal lower limb weakness → flaccid areflexic tetraparesis.

  * if patient performs mild exercise full-blown attack may be aborted ("walking 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 also decreased.
- attacks last 1-12 hours (occasionally up to 3 days).
- ***fatalities are rare*** (e.g. hypokalemia-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%);

  N.B. the only site of possible myotonia are eyelids!

  older subjects - persistent weakness (attributed to vacuolar myopathy).

DIAGNOSIS, DIFFERENTIAL DIAGNOSIS, MANAGEMENT – *see above >>*

If patient requires anesthesia, consider ***nondepolarizing neuromuscular blocker***.

Other / Possible Channelopathies

SCHWARTZ-JAMPEL syndrome (s. chondrodystrophic 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 waxing and waning (i.e. continuous high-frequency electrical activity).

DIAGNOSIS, DIFFERENTIAL DIAGNOSIS, MANAGEMENT – *see above >>*

THYROTOXIC PERIODIC PARALYSIS

- clinically often indistinguishable from HYPOKALEMIC PERIODIC PARALYSIS but with additional, sometimes subtle, hyperthyroidism.
  N.B. paralysis and hypokalemia may be profound, with *fatalities reported*!
- results from *alteration in muscle membrane permeability* (decreased activity of Ca^{2+} 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 thyrotoxicosis control is instituted.
  - acetazolamide does not prevent attacks.
  - acute attacks respond to **KCl**.

ANDERSEN'S SYNDROME

- rare **autosomal dominant** disorder with:

1) PERIODIC PARALYSIS (hypo-, hyper-, or normo-kalemic)
2) **dysmorphic features** (hypertelorism, low set ears, short stature)
3) prolonged QT interval, life-threatening **ventricular arrhythmias**.

BRODY'S DISEASE

- mutations in 16p12 - **sarcoplasmic reticulum Ca^{2+}-ATPase*** gene (esp. in type 2 muscle fibers).
  * extrudes Ca^{2+} 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.

CLINICAL FEATURES

- begins in childhood - **exercise-induced myotonia** (i.e. pseudomyotonia)
  - 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.

DIAGNOSIS

- no **EMG** abnormalities!!! (electrical silence during time of apparent myotonia)
- **myoglobinuria** occurs in some.
- **CK** normal or slightly↑.
- **muscle biopsy** - type 2A and B atrophy with angulated fibers.

TREATMENT – **DANTROLENE**, Ca-channel blockers.

RIPPLING MUSCLE DISEASE

- **autosomal dominant** mutations in 1q41 → localized **transient muscle swelling or rippling** induced by percussion or exercise (patients 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 → *HYPEREXCITABLE MOTOR NERVE* → ***continuous muscle fiber activity*** (persists even during sleep).

- continuous discharges may originate anywhere along length of peripheral nerve (abolished by curare but usually persist after general anesthesia).

ETIOLOGY

- **autoimmune**.

- sometimes associated with tumor (paraneoplastic syndrome), e.g. thymoma, small cell lung carcinoma, lymphoma.
- **autosomal dominant** form exists - **EPISODIC ATAXIA type I** - defect in K^+ channel.

see p. Mov50 >>

CLINICAL 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. see p. Mov3 >>, p. D20 >>
   *results in occasional muscle hypertrophy
2. Persistent or intermittent **ABNORMAL DISTAL**** **LIMB POSTURES** (identical to carpal or pedal spasm - ***finger clawing***, ***toe-walking***);
   **vs. stiff-person syndrome - proximal & axial muscles are affected most severely

   - later stiffness of **proximal & axial muscles**;
   - occasionally, oro-pharyngo-laryngeal or respiratory muscles are affected.
3. **STIFFNESS (PSEUDOMYOTONIA)** - clinically resembles true myotonia (voluntary contraction induces spasm that persists during attempted relaxation); no percussion myotonia.
4. Liability to **CRAMPS** with **HYPERHIDROSIS**.
5. Mild weakness, tendon reflexes↓.

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;

   No characteristic myotonic bursts ("dive bombers")!

   - 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 >>