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:

1. hyperexcitability → **myotonia**
2. 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!



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!

* + 1. **Dystrophic myotonias** (considered myodystrophies not channelopathies) - myotonia is one of several muscle symptoms, with **muscle atrophy & weakness** being most prominent:

[see p. Mus5 >>](http://www.neurosurgeryresident.net/Mus.%20Muscular%2C%20Neuromuscular%20disorders%5CMus5.%20Muscular%20Dystrophies.pdf)

* + - 1. Myotonic dystrophy (s. Steinert disease)
			2. Proximal myotonic dystrophy (s. Thornton-Griggs-Moxley disease)
		1. **Nondystrophic myotonias** - **myotonia** is most prominent symptom. [see p. Mus5 >>](http://www.neurosurgeryresident.net/Mus.%20Muscular%2C%20Neuromuscular%20disorders%5CMus5.%20Muscular%20Dystrophies.pdf)

**Diagnosis**

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

**EMG** – spontaneous myotonic discharges; [see p. D20 >>](http://www.neurosurgeryresident.net/D.%20Diagnostics%5CD20-29.%20Electrophysiology%20%28EEG%2C%20evoked%20potentials%2C%20MEG%2C%20EMG%2C%20nerve%20conduction%29%5CD20.%20EMG.pdf)

* 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:

1. Associated with **high / normal serum [K+]** (i.e. hyperkalemic periodic paralysis)
2. 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+, Ca2+, Mg2+, 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)!

1. **ECG** - hypokalemia / hyperkalemia.
2. **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.
1. **nerve conduction studies** – normal (exclude neurogenic causes); muscles do not respond to electrical stimulation during attack.
2. **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 >>](http://www.neurosurgeryresident.net/D.%20Diagnostics%5CD30-39.%20Biopsy%20%28brain%2C%20nerve%2C%20muscle%29%5CD30.%20Muscle%20Biopsy%20and%20Serum%20Markers.pdf)
1. **provocative testing** to produce weakness (under careful supervision):
2. ***hypokalemic challenge*** – i/v 100 g **glucose +** 20U regular **insulin** (to drive K+ into cells).
3. ***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**:
	1. **metabolic** – Ca2+↓↑, phosphate↓, Mg2+↓, rhabdomyolysis.
	2. **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):
	1. **renal** - juxtaglomerular hyperplasia (Bartter syndrome), renal tubular acidosis, Fanconi syndrome.
	2. **endocrine** - primary hyperaldosteronism (Conn syndrome), **thyrotoxic periodic paralysis** (see below)
	3. **gastrointestinal** – fistula, laxative abuse, villous adenoma, pancreatic noninsulin-secreting tumors with diarrhea, nontropical sprue.
	4. **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:
	1. **urinary K+ excretion promoters** - acetazolamide; alternatives - **thiazides**, fludrocortisone.
	2. **Na/K-ATPase activators** - **inhaled β-adrenergics** (e.g. salbutamol).
	3. *high-carbohydrate* / *low-potassium* diets.
	4. avoid fasting, strenuous activity, cold.

***Hypokalemic periodic paralysis***

* attack prophylaxis -acetazolamideup 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:

1. *inexcitability* → **hyperkalemic periodic paralysis** (exacerbated by extracellular K+↑).
2. *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* >>](#PERIODIC_PARALYSES)

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* >>](#MYOTONIAS)

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* >>](#MYOTONIAS)

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* >>](#MYOTONIAS)

Ca2+ channelopathies

Hypokalemic Periodic Paralysis

Genetics & Pathophysiology

- mutations in 1q31-32 - **α-1 subunit** of **voltage-sensitive** **Ca2+ 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* >>](#PERIODIC_PARALYSES)

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* >>](#MYOTONIAS)

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 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 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 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.

**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 >>](http://www.neurosurgeryresident.net/Mov.%20Movement%20disorders%2C%20Ataxias%5CMov50.%20Ataxias.pdf)

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 >>](http://www.neurosurgeryresident.net/Mov.%20Movement%20disorders%2C%20Ataxias%5CMov3.%20GENERAL%20-%20UMN%20%28pyramidal%29%20%26%20LMN%20Disorders.pdf), [p. D20 >>](http://www.neurosurgeryresident.net/D.%20Diagnostics%5CD20-29.%20Electrophysiology%20%28EEG%2C%20evoked%20potentials%2C%20MEG%2C%20EMG%2C%20nerve%20conduction%29%5CD20.%20EMG.pdf)

\*results in occasional muscle hypertrophy

* 1. 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.
	1. **Stiffness (pseudomyotonia)** - clinically resembles true myotonia (voluntary contraction induces spasm that persists during attempted relaxation); no percussion myotonia.
	2. Liability to **cramps** with **hyperhidrosis**.
	3. 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).
1. **nerve conduction** may be slow.
2. sural **nerve biopsy** may be abnormal.
3. **CK** can be mildly elevated.
4. **CSF** - elevated protein and oligoclonal bands.
5. specific **antibodies** in serum.

Treatment

1. **phenytoin**, **carbamazepine**.
2. immunosuppressive agents, plasmapheresis.

Bibliography for ch. “Neuromuscular, Muscular Disorders” → follow this [link >>](http://www.neurosurgeryresident.net/Mus.%20Muscular%2C%20Neuromuscular%20disorders%5CMus.%20Bibliography.pdf)

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