

# 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).

<b>SODIUM channel α-subunit (17q23-25)</b>
Hyperkalemic periodic paralysis:
with myotonia
without myotonia
with paramyotonia congenita
Paramyotonia congenita
Sodium channel myotonias:
Myotonia fluctuans
Myotonia permanens
Acetazolamide-responsive myotonia
<b>CHLORIDE channel (7q32)</b>
Autosomal dominant myotonia congenita (Thomsen)
Autosomal recessive myotonia congenita (Becker)
<b>CALCIUM channel α-1 subunit (1q31-32)</b>
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!

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<sup>+</sup>]** (i.e. hyperkalemic periodic paralysis)
- B. Associated with **low serum [K<sup>+</sup>]** (i.e. hypokalemic periodic paralysis).

\*abnormal serum [K<sup>+</sup>] is clearly consequence rather than cause of periodic paralysis!

**Diagnosis**

- 1) **serial blood tests** (during weakness episode) for K<sup>+</sup>, Ca<sup>2+</sup>, Mg<sup>2+</sup>, phosphate, CK.
  - each time blood sample is taken, *muscle strength* is tested.
  - K<sup>+</sup> levels are checked every 15-30 min to determine direction of change when muscle strength is decreasing or improving.
  - N.B. K<sup>+</sup> level may be normal during **hyperkalemic periodic paralysis** and occasionally in **hypokalemic periodic paralysis**.
  - N.B. between attacks of periodic paralysis, serum [K<sup>+</sup>] 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<sup>+</sup> 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	KCl load
Normokalemic	More severe and prolonged than hyperkalemic	KCl 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<sup>2+</sup> ↓↑, phosphate ↓, Mg<sup>2+</sup> ↓, rhabdomyolysis.
  - b) **neurologic** – Guillain-Barré syndrome, myasthenic syndrome, acute poliomyelitis.
- 2) **SECONDARY HYPOKALEMIC PARALYSIS** (results from intracellular K<sup>+</sup> depletion) – usually late-onset with marked hypokalemia (vs. PRIMARY form – rarely starts after age 30; serum [K<sup>+</sup>] 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<sup>+</sup> 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<sup>+</sup> channelopathies

### GENETICS & PATHOPHYSIOLOGY

- allelic point mutations in [17q23-25] - **α-subunit of voltage-dependent Na<sup>+</sup> channel gene (SCNA4A)** → **reduced inactivation of Na<sup>+</sup> channel**\* → increased muscle:

- inexcitability* → **HYPERKALEMIC PERIODIC PARALYSIS** (exacerbated by **extracellular K<sup>+</sup>↑**).
- 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 1<sup>st</sup> 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<sup>+</sup>]** usually rises during attack (K<sup>+</sup> 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<sup>-</sup> channelopathies

### GENETICS & PATHOPHYSIOLOGY

- allelic point mutations in [7q35] – **Cl<sup>-</sup> channel gene (CLC9I)** → **reduced membrane Cl<sup>-</sup> 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 1-2<sup>nd</sup> 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<sup>2+</sup> channelopathies

### HYPOKALEMIC PERIODIC PARALYSIS

#### GENETICS & PATHOPHYSIOLOGY

- mutations in [1q31-32] - **α-1 subunit of voltage-sensitive Ca<sup>2+</sup> channel (CACNL1A3, s. dihydropyridine receptor)\***.

\* primary role in electrocontraction coupling

Unknown mechanism causes **increased sensitivity to insulin** → **K<sup>+</sup> 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<sup>+</sup>] 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  $\text{Ca}^{2+}$  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!;  **$\beta$ -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  $\text{Ca}^{2+}$ -ATPase\* gene** (esp. in type 2 muscle fibers).
  - \* extrudes  $\text{Ca}^{2+}$  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  $\uparrow$ .
- **muscle biopsy** - type 2A and B atrophy with angulated fibers.

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

## RIPPLING MUSCLE DISEASE

- **autosomal dominant** mutations in **1q41**  $\rightarrow$  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  $\text{K}^+$  channels on peripheral nerves**  $\rightarrow$  channel inactivation  $\rightarrow$  **HYPEREXCITABLE MOTOR NERVE**  $\rightarrow$  **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  $\text{K}^+$  channel.

see p. Mov50 >>

### CLINICAL FEATURES

- begins insidiously in children  $\div$  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  $\downarrow$ .

### 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 >>](#)