Skeletal Muscle CHANNELOPATHIES

Last updated: September 5, 2017

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!

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	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^{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 >>