PERIODIC PARALYSIS

Differential Diagnosis and Important Diagnostic Tests

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How do people present?

- **Episodic weakness**
  - **Related to potassium**
    - **Hypokalemia**
    - **Hyperkalemia**
  - **Unrelated to potassium**
- Permanent weakness
- Episodic stiffness
- Episodic hyperkalemia
- Episodic hypokalemia

How should we organize our thoughts?

- **If it IS periodic paralysis, what type is it?**
- **If it IS NOT periodic paralysis, then what is it?**

Periodic Paralysis:
Episodic weakness related to potassium

Hypokalemic

- Familial
- Thyrotoxic
- Andersen-Tawil
- Normokalemic

Hyperkalemic

- Familial
- With Paramyotonia Congenita
- Andersen-Tawil
- Normokalemic

Not Periodic Paralysis:
Episodic Weakness related to episodic hypokalemia

Renal

- Renal tubular acidosis, Types 1 and 2
- Liddle's syndrome
- Bartter's syndrome
- Gitelman's syndrome
- Hypomagnesemia

Endocrine

- Hyperaldosteronism
- Hypercortisolemia
- 11-beta hydroxysteroid dehydrogenase deficiency
- Congenital adrenal hyperplasia

Ingested Substances

- Potassium-wasting diuretic abuse
- Barium poisoning
- Licorice intake (glycyrrhetinic acid)
- Surreptitious glue-sniffing or toluene intoxication
- Pseudoephedrine abuse

Physiologic

- Diarrhea
- Vomiting
- Excessive sweating

Not Periodic Paralysis:
Episodic Weakness related to episodic hyperkalemia

- Renal tubular acidosis, Type 4
- Hypoaldosteronism
- Potassium-sparing diuretic abuse

Not Periodic Paralysis:
Episodic Weakness unrelated to potassium

- Myotonia congenita
- Myasthenia gravis
- Congenital myasthenic syndromes
- Sleep paralysis
- Narcolepsy/Cataplexy
- Epilepsy (focal seizures)
- Episodic ataxia

Periodic Paralysis:
Permanent weakness

Hypokalemic

- Familial
- Thyrotoxic?
- Andersen-Tawil
- Normokalemic

Hyperkalemic

- Familial
- With Paramyotonia Congenita
- Andersen-Tawil
- Normokalemic

Not Periodic Paralysis: Permanent Weakness

- Congenital myasthenic syndromes
- Myotonic dystrophy type 1 (DM1)
- Muscular dystrophies
- Myasthenia gravis - rarely

Periodic Paralysis:
Episodic Stiffness

- Hyperkalemic periodic paralysis
- Hyperkalemic periodic paralysis with paramyotonia congenita
- Hypokalemic periodic paralysis, familial (rare, usually sodium-channel)
- Andersen-Tawil Syndrome

Not Periodic Paralysis: Episodic Stiffness

Ion Channelopathies

- Paramyotonia congenita (PMC)
- Myotonia congenita
- Potassium-aggravated myotonia

Other

- Myotonic dystrophy type 1 (DM1)
- Epilepsy (focal seizures)
- Brody myopathy
- Schwartz-Jampel syndrome
- Myotonic dystrophy type 2 or proximal myotonic myopathy (PROMM)
- Stiff-Person Syndrome
- Isaacs syndrome (neuromyotonia)

Important Diagnostic Tests

- **Electrolyte Panels**
- **Genetic testing**
- **Long Exercise Test**
- **Routine EMG**
- **EKG**
- **Muscle Biopsy**
- **Routine Hydrogen-MRI**
- **CT Scan Without Contrast**
- **Sodium-MRI**
- **Exercise Challenge Test**
- **Fasting Challenge Test**
- **Cold Challenge Test**
- **Glucose/Insulin Challenge Test**
- **Potassium Challenge Test**
- **Serum Creatine Phophokinase (CK)**
- **Thyroid function tests**

Other Diagnostic Tests

- **EEG**
- **Urinalysis** – spot and 24-hour for potassium, calcium, phosphorus, magnesium, and pH
- **Urine diuretic screen and Stool magnesium (laxative abuse)**
- **Endocrine/Renal Tests**:
  - Serum aldosterone
  - Serum renin
  - Serum random cortisol
  - Cosyntropin stimulation test

Other Diagnostic Tests, cont.

- **Genetic tests for**:
  - Bartter's
  - Gitelman's
  - RTA 1
  - RTA 2
  - Liddle's syndrome
- **Myasthenia gravis**: check anti–acetylcholine receptor (AChR) antibodies
- **Narcolepsy**: overnight polysomnogram followed by a multiple sleep latency test (MSLT); CSF hypocretin
- **Stiff Person Syndrome**: serum anti–glutamic acid decarboxylase (GAD) antibodies
- **Myotonic dystrophy types 1 and 2**: CTG repeats in the DMPK gene for type 1 and CCTG repeats in the *CNBP* (*ZNF9*) gene for type 2

Electrolytes: really, potassium

- **Potassium during attack**
  - Low – usually hypoPP
  - High – hyperPP
  - Normal – leaves us guessing
- **Pitfalls**:
  - Tourniquet left on too long elevates potassium
  - Hemolysis elevates potassium

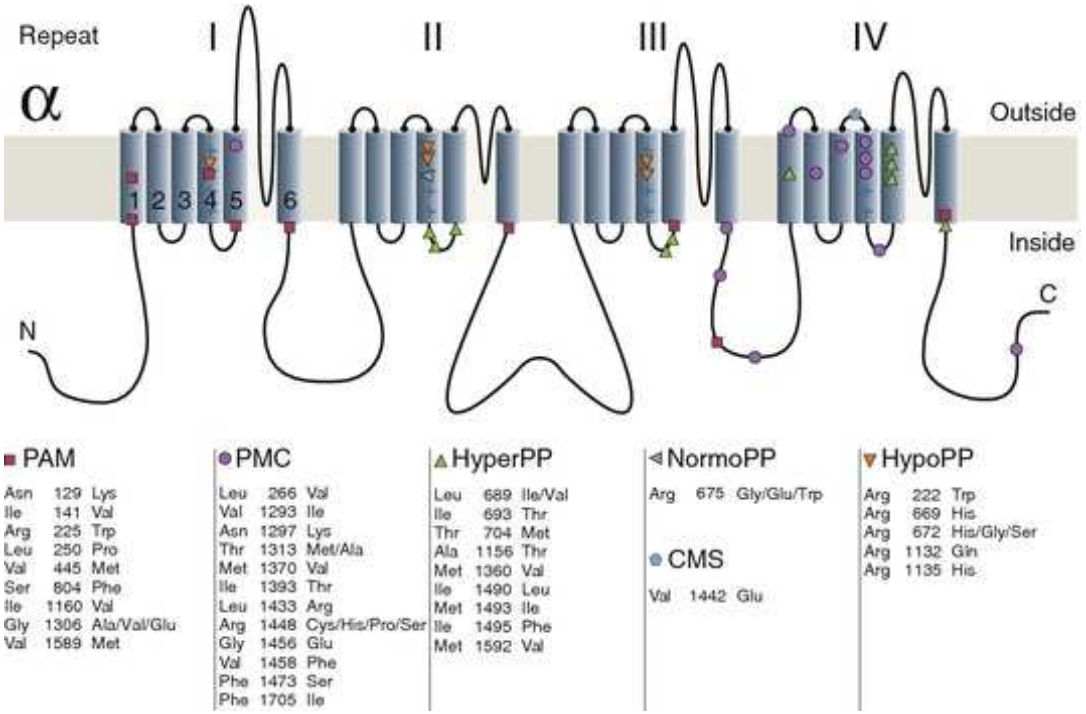
- If sodium is always low or always high, suspect adrenal gland dysfunction
  - High sodium, low potassium: Conn syndrome, Cushing syndrome
  - Low sodium, high potassium: Addison disease, congenital adrenal hyperplasia

Genetic testing

- Gold standard for diagnosis
- Negative test does NOT rule out
  - You may have an as of yet undescribed mutation
  - **Up to 30% of patients are mutation negative!**

Genes causing Periodic Paralysis

- **Sodium channel**
  - Hyperkalemic PP +/- PMC
  - PMC
  - Hypokalemic PP type 2
  - Potassium aggravated myotonia
- **Calcium channel**
  - Hypokalemic PP
- **Potassium channel**
  - Andersen-Tawil Syndrome
  - Thyrotoxic PP
- **Chloride channel**
  - Myotonia congenita



Long Exercise Test (aka McMannis test)

- Name derives from long recording period, not duration of exercise
- Place electrode on side of hand below pinky
- Record baseline CMAP (measures electricity muscle produces) and with 10 cycles of squeezing for 25 sec / 5 sec rest (i.e., 5 min)
- Record CMAP during the 5 sec rest periods then every minute for 10 minutes post exercise then every 2 minutes for 40 minutes (i.e., test takes 55 minutes)
- **Positive in 80%** of periodic paralysis patients (hyperPP, hypoPP, or ATS)
  - abnormally depressed CMAPs after exercise signify inability of muscle to recover/become excitable after exercise
- **Negative test does not rule out periodic paralysis**

NEGATIVE

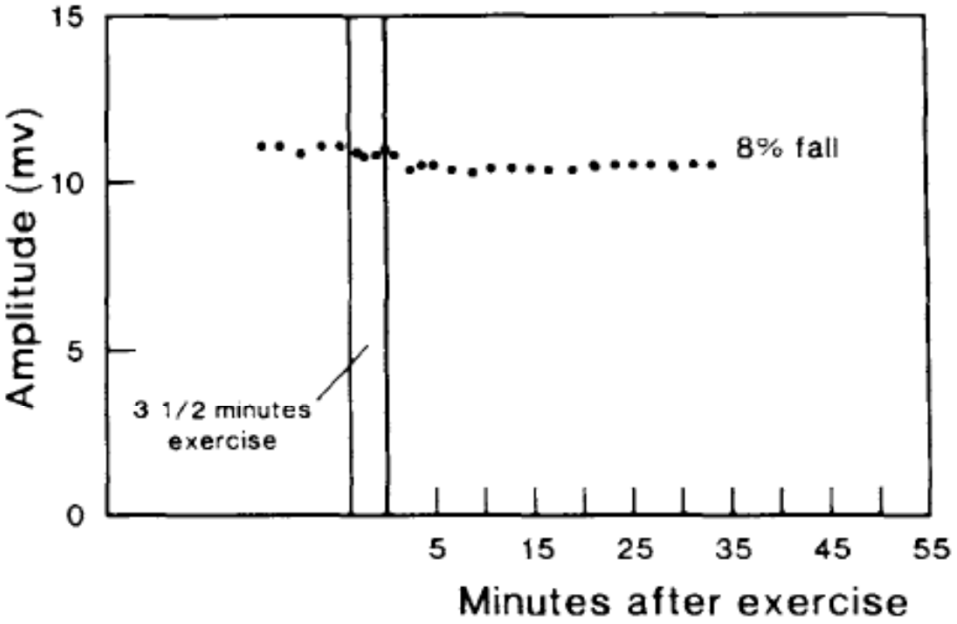


FIGURE 1. Amplitude of hypothenar compound muscle action potential recorded before, during, and after maximal voluntary contraction of hypothenar muscles in a normal subject. The ulnar nerve was stimulated supramaximally at the wrist. Dots indicate amplitude in response to a single stimulus.

POSITIVE

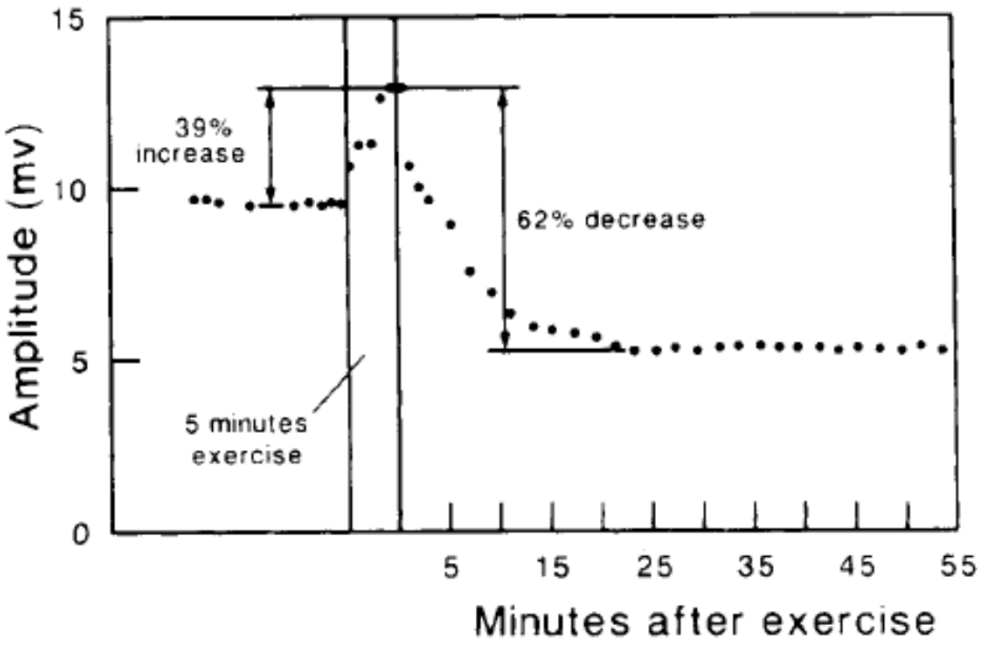


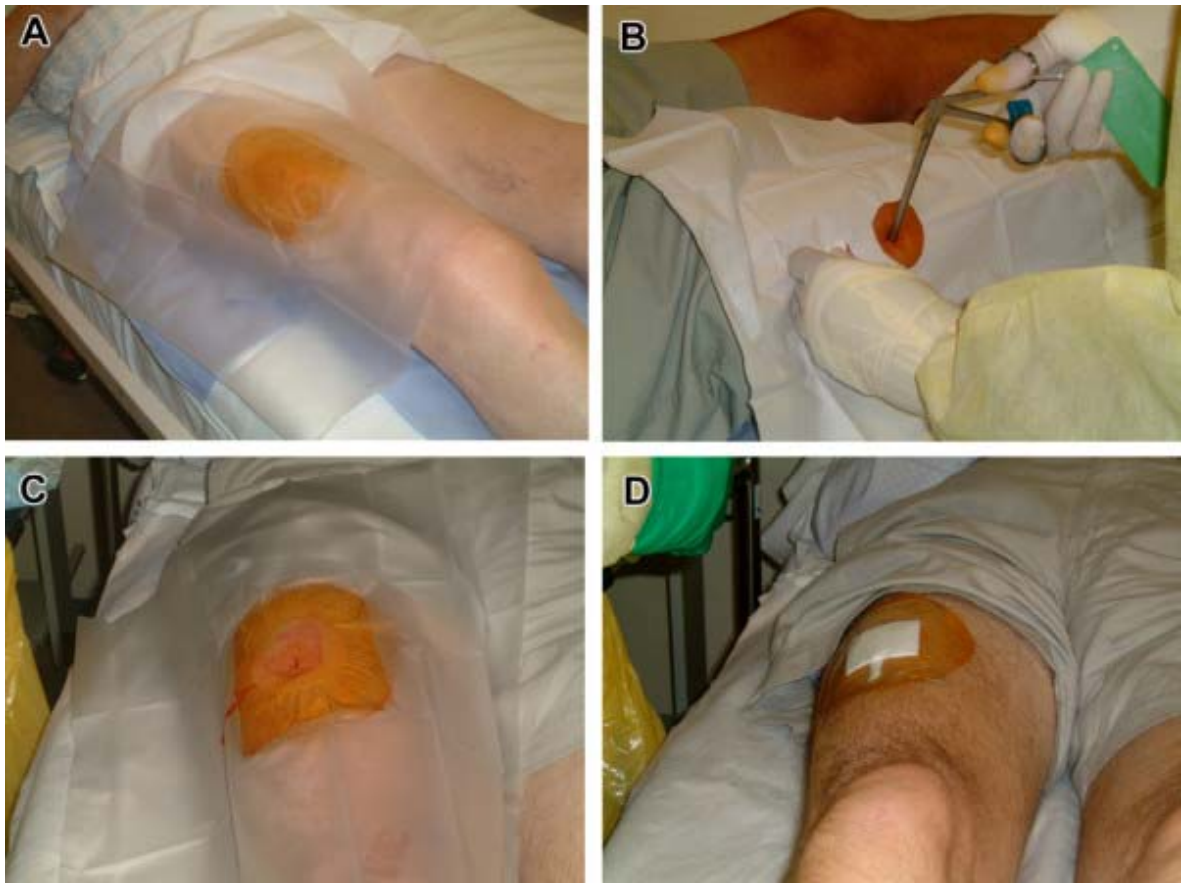
FIGURE 3. Effect of exercise on amplitude of compound muscle action potentials in a patient with primary periodic paralysis. Dots indicate amplitude in response to a single stimulus.

McManis et al. The exercise test in periodic paralysis. Muscle Nerve. 1986 Oct;9(8):704-10.

Muscle Biopsy

- Biopsy from thigh in a moderately affected area as identified by MRI
  - Avoid where muscle is replaced by fat/connective tissue
- Non-specific
  - i.e., also seen in inclusion body myositis, McArdle myopathy, Danon disease, and X-linked myopathy
- Does not distinguish type of PP
  - Same changes seen in hypoPP, ATS, TPP, hyperPP, and PMC.
- Normal biopsy does NOT rule out disease

Muscle Biopsy



Muscle Biopsy

- When positive, biopsy shows:
  - vacuolization and sarcoplasmic masses filled with PAS positive material
  - atrophy of single muscle fibers and some central nuclei
  - vacuoles best observed a few weeks after a severe attack of weakness
- Vacuolar myopathy can be independent of attacks
- Permanent Muscle Weakness shows conversion of myocytes to fibrosis and fat
  - seen also in limb girdle dystrophy

Vacuolar Myopathy in Periodic Paralysis

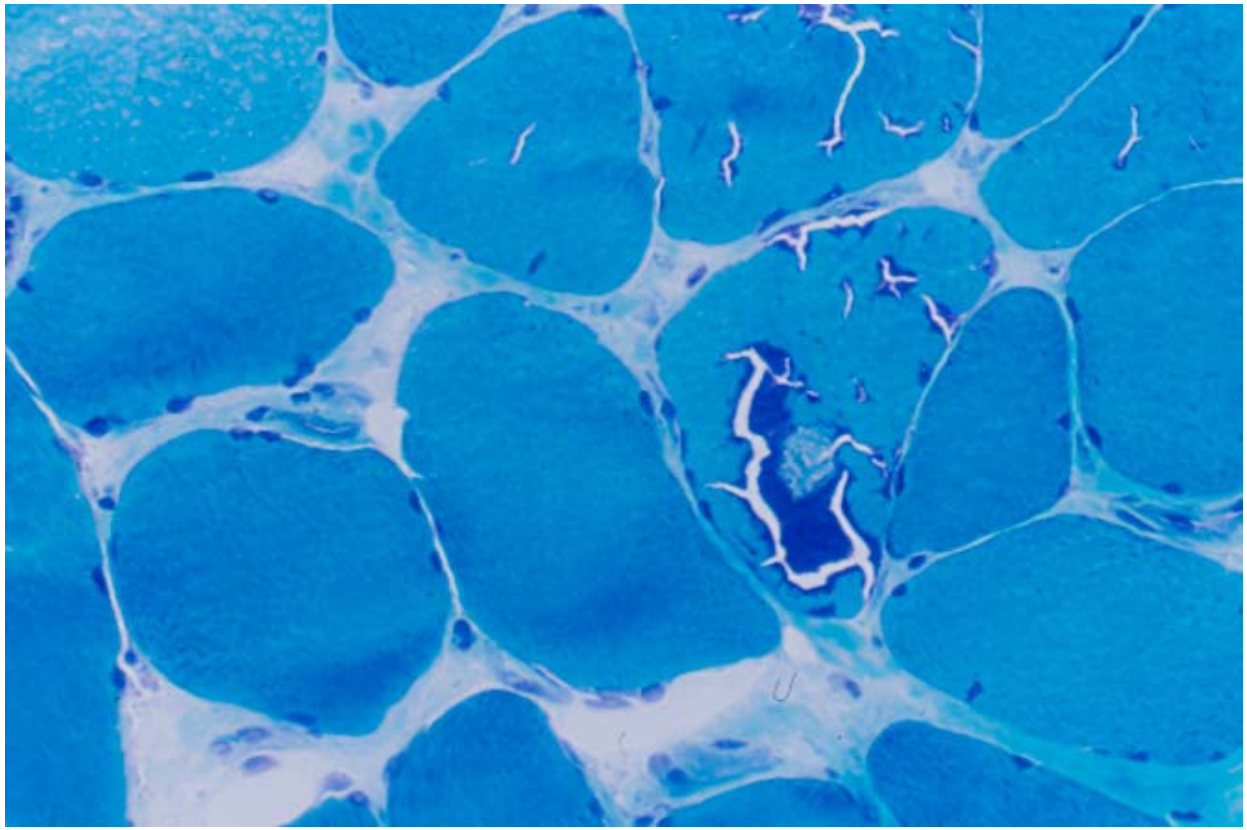


Photo courtesy of Dr. Rabi Tawil, University of Rochester Medical Center, NY

Photo courtesy of Dr. Frank Lehmann-Horn

Routine Hydrogen-MRI

- Quantifies fibrofatty degeneration in PMW
- Quantifies pathologic muscle edema
  - marker of reversibility of fixed weakness
  - Consistent with inflammation and osmotic edema (during acute attacks)
- T1-weighted images can resolve muscle, fat, connective tissue, and bone
- Need fat-suppression method to differentiate between fat and water

Sodium-MRI

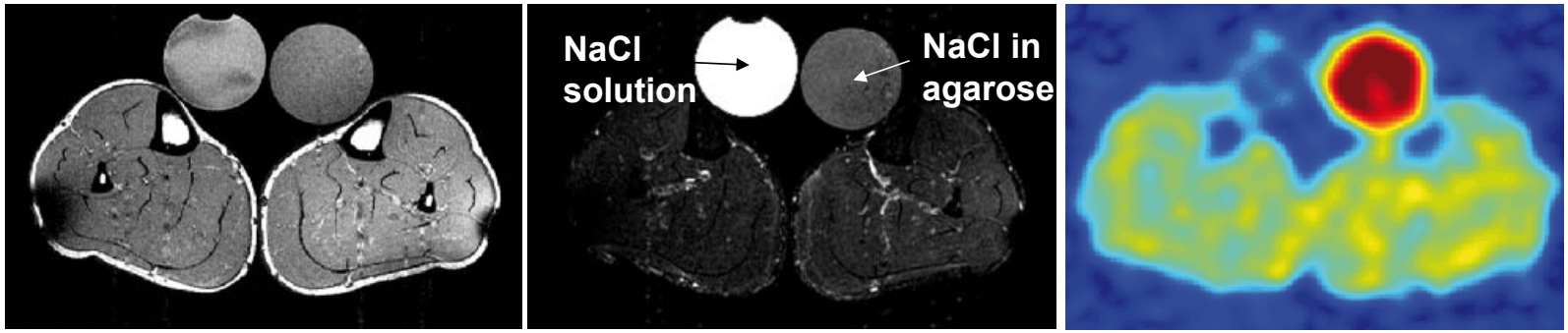
- Not available in most centers
- Can quantify the myopathy in periodic paralysis
- Diseased muscle has more sodium than normal muscle

Slide taken from Dr. Frank Lehmann-Horn 2011 PPA talk

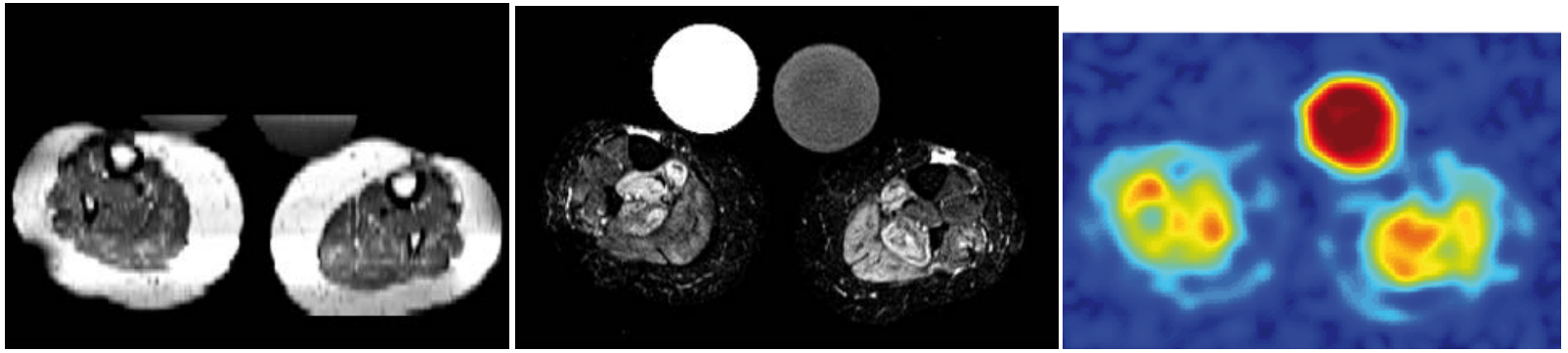
Novel technique: ^{23}Na-MRI IR

Control: low muscle Na^+_i content

^{1}H-T1 | ^{1}H-T2-STIR | ^{23}Na-IR

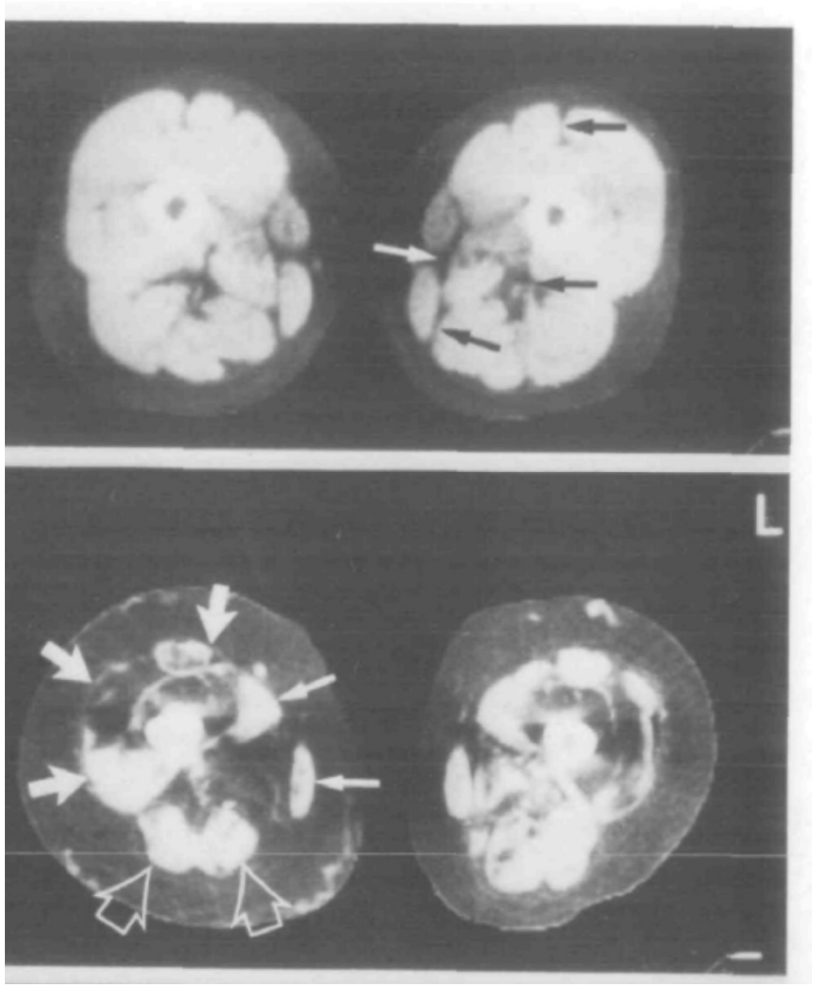


HypoPP with permanent weakness: dystrophy, edema and intracellular Na^+ accumulation



CT Scan Without Contrast

- Shows fatty replacement of muscle
- Shows extent of permanent muscle weakness
- Less sensitive than MRI
- Cannot detect or quantify muscle edema
  - Ultrasound can help here but MRI is best



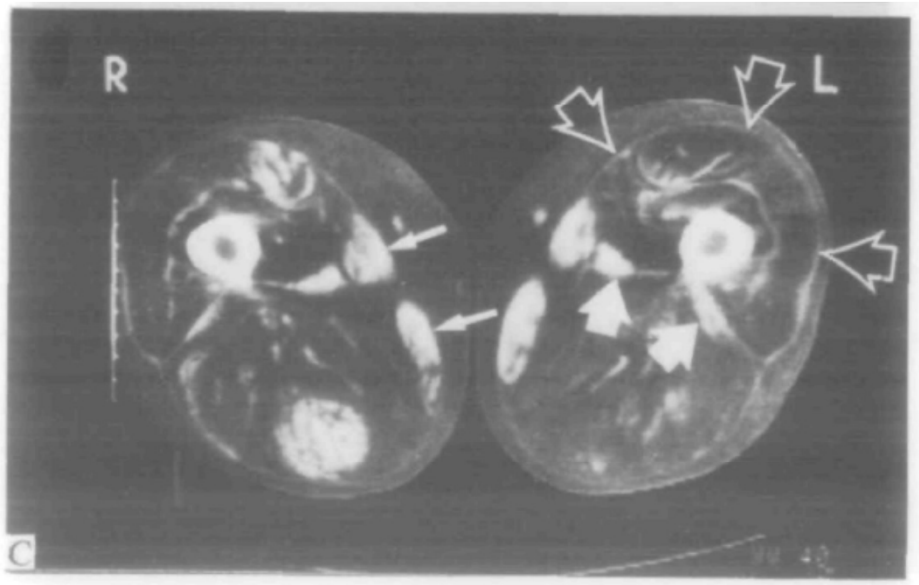


FIG. 2. Examples of various grades of muscle involvement in CT scans. A, *Case 2*. Normal appear signs of replacement of muscle tissue by fat (grade 0). Normal fat planes and areas between muscle gro by arrows. B, *Case 8*. Minimal involvement of sartorius and gracilis (small arrows, grade 1). Involve than 50% in quadriceps (large arrows, grade 3). Posterior groups show approximately 50% involvement (Note some differences in severity between left and right; this impedes completely accurate and reprod C, *Case 10*. Clear involvement of sartorius and gracilis muscles but less than 50% affected (small arro Severe involvement of more than 50% in posterior groups (grade 3), subtotal: only central areas at left are arrows). Virtually total involvement of quadriceps at left (open arrows, grade 4).

Links TP, Zwarts MJ, Wilmink JT, Molenaar WM, Oosterhuis HJ. **Permanent muscle weakness in familial hypokalaemic periodic paralysis. Clinical, radiological and pathological aspects.** 1990 Dec;113 (Pt 6):1873-89.

Exercise Challenge Test

- Tests for hyperPP, hypoPP, or PAM
- No evidence-based protocol exists
- Outpatient setting involving 30 minutes of vigorous exercise
  - Stationary bike safer than treadmill if sudden weakness occurs
  - Target heart rate of 120-160 beats per minute, followed by bed rest
- Monitor for attack for at least 2 hours after the challenge
- Measure serum potassium at baseline and during attack of weakness
- Serum potassium rises during exercise then falls to normal as in healthy individuals.
- After 10-20 minutes of rest:
  - a second, pathologic hyperkalemia occurs in hyperPP → paralysis, or,
  - hypokalemia occurs in hypoPP → paralysis

Cold Challenge Test

- Tests for hyperPP or PMC
- No standard protocols exist
- Submerge both hands and forearms into cold water of 15^{o}C/59^{o}F for 30 minutes to trigger attack
- Measure serum potassium at baseline, 30 minutes after the test has been completed, and during an attack
- Conduct EMG on cold-induced stiff muscle

Fasting Challenge Test

- Tests for hyperPP, PMC, or PAM
- No evidence-based protocol exists
- 12-18 hours of fasting with only water by mouth permitted
- Inpatient setting with i.v. access in place
- After fasting, try to trigger attack with light exercise
  - stationary bicycle, push-ups, squats, climbing stairs or running in place for five minutes, or treadmill
  - Avoid treadmill with history of sudden weakness
- Monitor serum potassium every 4 hours during fasting, 30 minutes after fasting, and during attack

Potassium Challenge Test

- Used to diagnose hyperPP, PMC, or PAM
- **Risk of fatal arrhythmia**
- Only performed when safer tests are inconclusive
- Only do in telemetry unit or medical intensive care unit
- No evidence-based protocol exists

Potassium Challenge Test: How To Do It

- Do in the morning in the fasting state
- Monitor ECG
- Have anesthesiologist on hand (in case respiratory failure)
- Contraindicated in patients already hyperkalemic or without adequate renal or adrenal reserve.
- Initially only the effects of 2 hours bed rest after 30 minutes of exercise are evaluated (see Exercise Challenge Test below).
- If weakness does not ensue, then the patient exercises again for 10 minutes and 2 g (27 mEq) oral potassium chloride is administered in an unsweetened solution just after exercise, and the patient then rests.
- If weakness does not supervene, additional doses of 2g (27 mEq) are given as single oral boluses every 30 minutes until weakness, arrhythmia, serum potassium level of 6.0mEq/L, or a total dose of 10g (133mEq) supervene.
- Serum potassium levels are determined at baseline and 15 minutes after each dose of potassium, 2 hours after the last dose, and during any attack of weakness that occurs.
- The provocative test usually induces an attack within an hour, and the induced attack lasts for 30 to 60 min, resembling spontaneous attacks of weakness.
- Monitor patient for at least 2 hours following the last dose of potassium for hyperkalemia, a hyperPP attack, or for arrhythmia

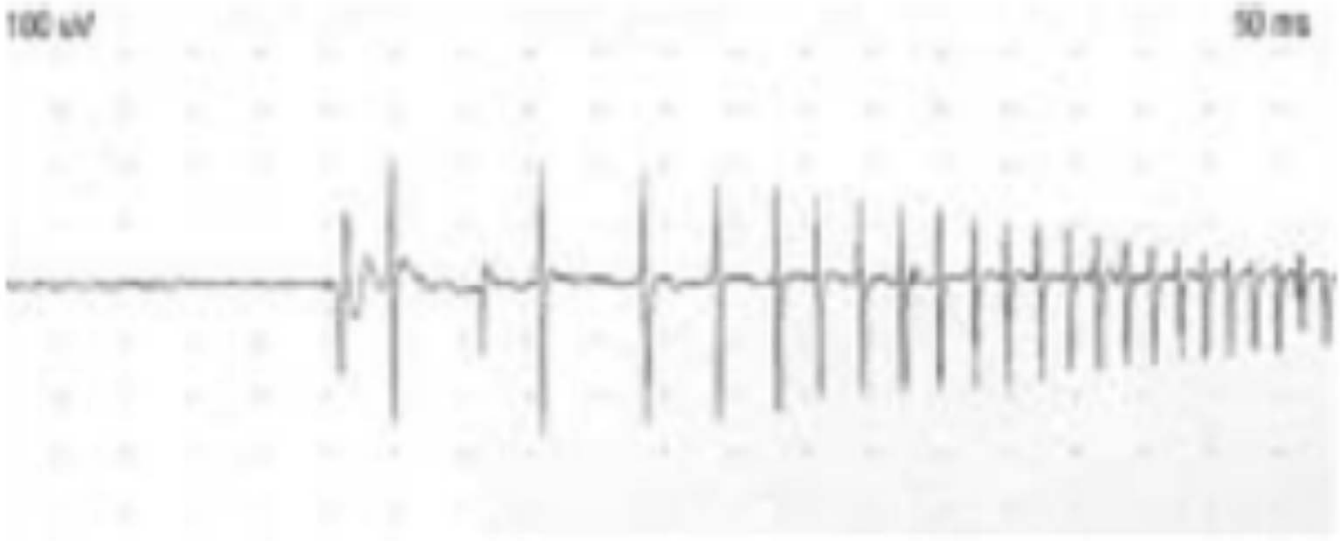
Glucose/Insulin Challenge Test

- Tests for hypoPP
- Dangerous due to **potential for fatal hypoglycemia** and **profound hypokalemia** and weakness, leading to **arrhythmia** and respiratory failure.
- Only performed when safer tests are inconclusive
- Only in telemetry unit or medical intensive care unit with stand-by anesthesia

Glucose/Insulin Challenge Test: How To Do It

- Testing in early morning when serum cortisol is high may facilitate a positive result
- Exercise and intake of carbohydrates the evening before increase the sensitivity of the test
- Infusion of glucose is more effective than oral ingestion
- Insulin subcutaneously or infusion
  - Infusion gives tighter control of dosing
- Glucose 1.5 - 3 g/kg is administered intravenously over 60 min combined with an intravenous insulin bolus in doses not exceeding 0.1 U/kg at 30 and 60 min.
- Paresis normally appears within 3 to 5 hrs.
- Monitor for clinical signs of hypoglycemia. Finger stick blood sugar checks should occur at 45, 60, 90, 120, and 180 min and during clinical signs of hypoglycemia.
- Potassium should be measured at 60, 120, and 180 minutes and during episodes of weakness.

Routine EMG – helpful to confirm myotonia



Salves myotoniques au repos dans le muscle long péronier latéral.

Sallansonnet-Froment M, Bounolleau P, De Greslan T, Ricard D, Taillia H, Renard JL. **Eulenburg's paramyotonia congenita].** Rev Neurol (Paris). 2007 Nov;163(11):1083-90.

Electrocardiogram (EKG, ECG)

- Helpful during attacks to identify arrhythmia
- Helpful between attacks when looking for long QTc in ATS

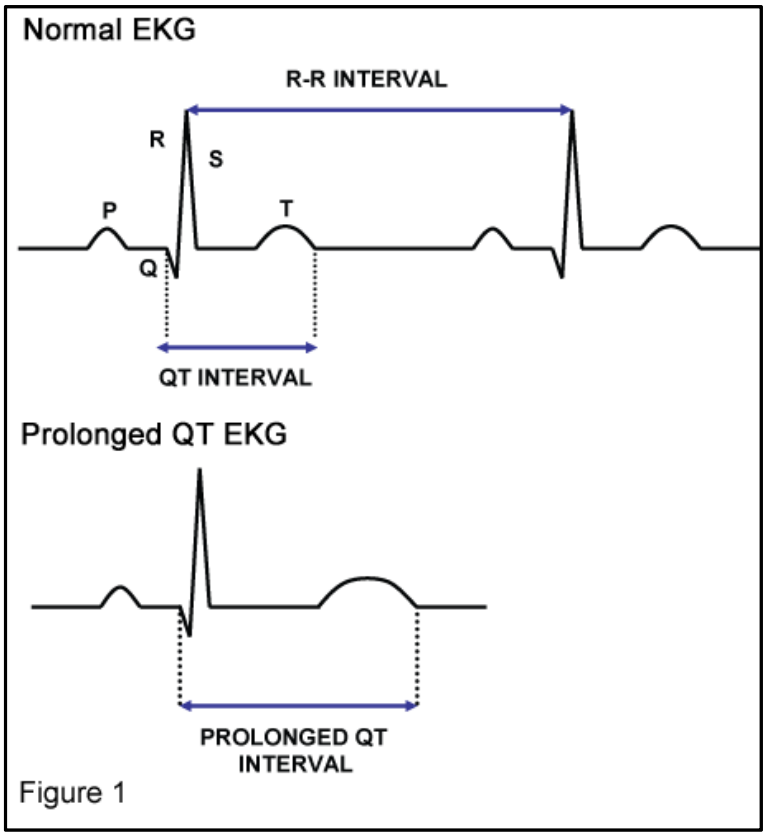


Figure 1

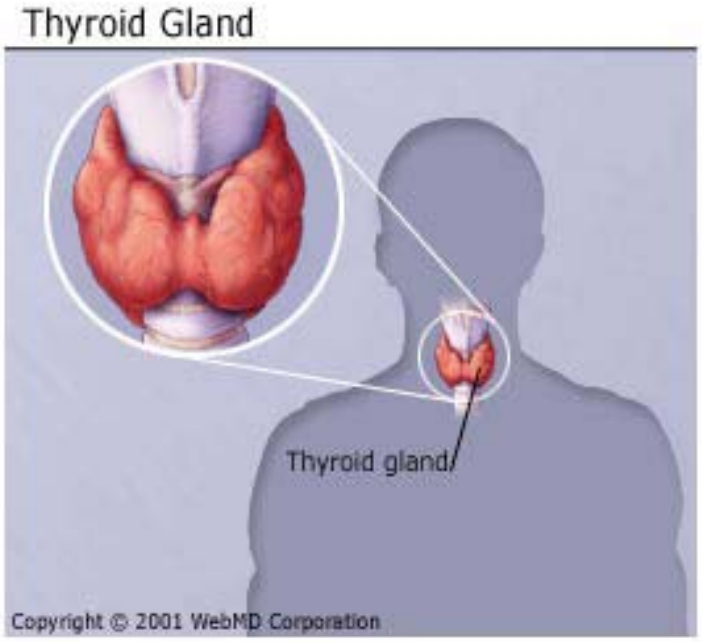
Serum Creatine Phosphokinase (CK)

- Elevated when muscle is damaged, i.e., with attacks of paralysis

Thyroid function tests

- Hyperthyroidism can unmask thyrotoxic periodic paralysis

- TSH will be low
- Free T4 or total T3 will be elevated



Proposed Diagnostic Criteria: HypoKPP

- Low serum K+ during attack of weakness, on more than a single occasion, frequently preceded by a known trigger

AND

- Strength returns with K+ intake or normalized serum K+.

OR

- Positive genetic testing for mutations of the SCN4A/$Na_v1.4$ sodium channel or CACN1AS/$Ca_v1.1$ calcium channel

Proposed Diagnostic Criteria: HyperPP

- Elevated serum K+ during an attack of weakness on more than a single occasion, frequently preceded by a known trigger

AND

- Return of strength with measures that reduce serum K+ or with normalized serum K+
- **OR**
- Positive genetic testing for the following mutations of the SCN4A $Na_v1.4$ sodium channel

Proposed Diagnostic Criteria: ATS

- **Periodic paralysis** (most often hypoPP, but can be hyperPP).

AND Either A or B must be met:

- A. One of the following two criteria:
  - 1) **cardiac arrhythmias / prolonged QTc** , or
  - 2) **characteristic physical anomalies**
    - characteristic facies, dental anomalies, small hands and feet, and at least two of the following: low-set ears, widely spaced eyes, small mandible, fifth-digit clinodactyly, syndactyly
- B. One of the above three (i.e., periodic paralysis, arrhythmia, or morphology) in addition to at least one other **family member** who has periodic paralysis and meets one of the two criteria of arrhythmia or morphology

OR Both:

- The presence of a **pathogenic KCNJ2 sequence** variant in conjunction with any sign or symptom (atypical episodic weakness, periodic paralysis, arrhythmia, or morphology).
- Negative genetic testing for the known mutations of the SCN4A/Na_v1.4 sodium channel or CACN1AS/Ca_v1.1 calcium channel responsible for familial hypoPP (see Genetic Testing below).

Maybe Periodic Paralysis if:

- Prevention of attacks with prophylactic medication
  - HypoPP: Potassium, Carbonic anhydrase inhibitors, Potassium-sparing diuretics
  - HyperPP: Carbonic anhydrase inhibitors or potassium-wasting diuretics
  - ATS: meds that help periodic paralysis
- Depressed CMAP on exercise nerve conduction study
- Positive Challenge Tests:
  - Hypo: exercise, glucose, or glucose/insulin
  - Hyper: exercise, cold, fasting, or potassium
  - ATS: exercise, glucose, glucose/insulin, potassium, cold, or fasting
- EMG during paralysis with electrically silent muscle; if stiffness is present, electrical myotonia
- Muscle biopsy with vacuolization
- Elevated muscle creatine phosphokinase
- Ruled out other causes of episodic hypokalemia or episodic or fixed weakness or TPP

What if Diagnostic Criteria are not met?

- Empiric Therapy?
- Entertain another diagnosis?

THANK YOU FOR YOUR ATTENTION!!!