Periodic Paralysis
&
Non-dystrophic Myotonia

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Clinical & Genetic Spectrum of the Primary Skeletal Muscle Channelopathies

Hanna et al, Curr Opin Neurol 2014

- SCM (SCN4A)
- ADMC (CLCN1)
- ARMC (CLCN1)
- PMC (SCN4A)
- HyperPP (SCN4A)
- HypoPP II (SCN4A)
- HypoPP I (CACNA1S)
- ATS (KCNJ2, KCNJ5)

Myotonia

Weakness or flaccid paralysis
Hereditary Periodic Paralysis – Common Features

- Symptoms typically start in 1st 2 decades of life
- Autosomal dominant inheritance
- Identifiable triggers
- Often associated with changes in extracellular potassium (high or low)
- Initially normal strength between attacks, but often a fixed proximal weakness
- Reduction of attack frequency or severity with carbonic anhydrase inhibitors
HyperPP – Clinical Features

- Attacks of variable severity
  - Mild weakness to profound paralysis
  - Duration: 1-4 hours (infrequently days)
- Triggers
  - Rest after exercise
  - Stress/fatigue
  - K-rich foods
- Potassium levels during attacks may be elevated or normal
- Bulbar & and respiratory muscles – rarely in severe attacks
- Fixed weakness
- Lifetime morbidity
Triggers in HyperPP

- Cold 75%
- Rest after exercise 67%
- Stress or fatigue 47.3%
- ETOH 45.1%
- Hunger 42.9%
- Changes in activity level 40.7%
- Potassium containing foods 35.2%
- Changes in humidity 35.2%
- Pregnancy 27.9% (of female respondents)
- Illness of any type 27.5%
- Menstruation 18.6% (of female respondents)
HypoPP – Clinical Features

- Attacks of variable severity
  - Mild weakness to profound paralysis
  - Duration: hours to days

- Triggers
  - Carbohydrate-rich foods, stress, alcohol, rest after exercise

- Potassium levels during attacks can decrease to <3.0 mmol/L.

- Ocular, bulbar, and respiratory muscles – rarely in severe attacks

- Fixed weakness

- Lifetime morbidity
Andersen-Tawil Syndrome

- ATS is a rare autosomal dominant disorder
  - Prevalence of approximately 1:1,000,000
- Clinical triad
  - Episodic flaccid muscle weakness, in the setting of high, low, or normal potassium
  - Ventricular arrhythmias & prolonged QT interval
  - Dysmorphic features
- Approximately 60% of patients with ATS have a mutation in a potassium inward rectifier KCNJ2 on chromosome 17
Characteristic Features
EKG – prolonged QT interval

Normal EKG

R-R INTERVAL

P Q R S T

QT INTERVAL

Prolonged QT EKG

PROLONGED QT INTERVAL

Figure 1
## Secondary Causes of HypoPP

<table>
<thead>
<tr>
<th>Renal</th>
<th>Ingested Substances</th>
<th>Endocrine</th>
<th>Physiologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal tubular acidosis, Types 1 &amp; 2 • Liddle’s syndrome • Bartter’s syndrome • Gitelman’s syndrome • Hypomagnesemia</td>
<td>Potassium-wasting diuretic abuse • Barium poisoning • Licorice intake • Gluesniffing or toluene intoxication • Pseudoephedrine abuse</td>
<td>Hyperaldosteronism • Hypercortisolemia • 11-beta hydroxysteroid dehydrogenase deficiency</td>
<td>Diarrhea • Vomiting • Excessive sweating</td>
</tr>
</tbody>
</table>
Secondary Causes of HyperPP

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

- Electrolyte Panel
- CPK
- Thyroid function tests
- Prolonged exercise test
- EMG
- EKG
- Muscle biopsy
- Genetic testing
- Urinalysis – spot and 24-hour for potassium, calcium, pH

Endocrine/Renal Tests
- Serum aldosterone
- Serum renin
- Serum random cortisol
- Cosyntropin stimulation test
Prolonged exercise test

McManis et al, Muscle & Nerve 1986
Fournier et al, Ann Neurol 2004

- Ulnar nerve recording over the hand
- Baseline CMAP recording (stimulus response)

- Exercise
  - Patient spreads the little finger against resistance for 5 mins
  - 3-4 sec rest period every 15 secs
  - Stimulate the nerve every 1 min during exercise period
- Stimulate nerve to record response every 1-2 mins x 30-50 mins
CMAP changes following long exercise in an unaffected patient (A), a patient with hyperkalemic periodic paralysis (hyperKPP) and T704M sodium channel mutation (B), a patient with hypokalemic periodic paralysis (hypoKPP) and R528H calcium channel mutation (C), a patient with Andersen-Tawil syndrom (ATS) and T309I potassium channel mutation (D). Pre-exercise (top trace) and post-exercise recordings (below) at different times following the trial (Ex) as indicated left to the traces. Scale between 2 dots: 5 ms, 5 mV.

Muscle Biopsy – mostly normal
Muscle Biopsy - hypoPP

- Tubular aggregates

- Vacuoles

http://neuromuscular.wustl.edu/pathol/hopp.htm
Diagnosis of PP

Diagnosis is based on

- Clinical history of attacks of flaccid paralysis
- Exclusion of secondary causes
- Positive family history
- Characteristic changes in serum potassium during attack (high or low)
- Characteristic reduction in CMAP amplitude on prolonged exercise test
- Genetic testing
Principles of Management of PP

- General principles
  - Identify triggers
  - Abortive therapy
  - Prophylactic therapy
  - Lifestyle adaptations
  - Genetic counseling
- HypoPP
  - Frequent small meals, low salt, low carbohydrate diet; avoidance of alcohol
- HyperPP
  - Avoid potassium-rich foods & fasting; oral carbohydrate snacks
HypoPP – Acute Treatment

- **Potassium:**
  - Oral potassium: 0.5 – 1 mEq/kg; not to exceed 200 mEq/day
  - Intravenous potassium: 40 mEq/L in 5 % mannitol solution to run at 10 mEq/h (maximum of 20 mEq/h); not to exceed 200 mEq/day

- **Contraindications**
  - Hyperkalemia, renal disease, untreated Addison’s disease

- **Main side effects**
  - Cardiac arrhythmias, osmotic diarrhea, paresthesias, burning sensation in the infused vein with intravenous potassium

- **Special points**
  - 20 mEq KCl orally → 0.5 mEq K+ in blood
  - Avoid potassium in saline or glucose infusions as these solutions can worsen paralysis in hypoPP
  - Severe attacks requiring repeat interventions should be monitored on telemetry
HyperPP – Acute Treatment

- **Dietary**
  - Oral carbohydrate up to 2.0 gm/kg

- **Beta agonists**
  - Mechanism: mostly likely stimulation of the Na-K pump with lowering of serum potassium and reduction of the sodium influx into the muscle fiber
  - Standard dosage 1 – 2 puffs inhalation 0.1 mg salbutamol or albuterol
  - Contraindications: high blood pressure during pregnancy, uterine infection, miscarriage, heart disease, & hypersensitivity
  - Main side effects: tremor, anxiety, headache, muscle cramps, dry mouth, & palpitations

- **Calcium gluconate i.v. in severe episode**
Prophylactic Treatment - PP

- Acetazolamide (Diamox)
  - Hanna et al, 2011: About 50% response rate (Calcium channel>Sodium channel)
  - Worsening in few SCN mutations
- Standard dosage 125 – 1,000 mg per day
- Contraindications
  - Hypersensitivity, renal disease, liver disease, adrenocortical insufficiency, metabolic acidosis & hypokalemia
- Main side effects
  - Bone marrow depression, drowsiness, paresthesias, kidney stones, and skin lesions
- Special points
  - Monitoring of acetazolamide should include complete blood count & electrolyte levels
Prophylactic Treatment - PP

- **Dichlorphenamid** (Keveyis)
  - FDA-approved 2015
  - Reduces attacks of PP
    - 9-week trial in adults with hyperPP (n=21) & hypoPP (n=44)
- **Standard dosage** 50 – 200 mg/day
- **Precautions**
  - Hypersensitivity, renal disease, liver disease, adrenocortical insufficiency, metabolic acidosis & hypokalemia
- **Main side effects**
  - Milder side effects compared to acetazolamide
  - Paresthesia, cognitive disorder, dysgeusia, & confusional state
Prophylactic Treatment - hypoPP

- **Eplerenone (Inspra)**
  - Aldosterone antagonist
  - Dosage 25-50 mg/day
  - Avoid in renal disease & type 2 diabetes with microalbuminuria

- **Triamterene (Dyrenium)**
  - Potassium-sparing diuretic
  - Standard dosage 50 – 150 mg per day

- **Spironolactone (Aldactone)**
  - Potassium-sparing diuretic
  - Dosage 50 – 150 mg per day
  - Side effect: breast enlargement & tenderness

- **Amiloride (Midamor)**
  - Dosage 5-20 mg/day
  - Avoid in renal disease & diabetes
Prophylactic Treatment - hyperPP

- **Hydrochlorothiazide**
  - Potassium-wasting diuretic
  - Upto 25 mg/day
Thyrotoxic Periodic Paralysis

- K channel defect
- Asians; male predominance
- Triggers
  - High carbohydrate load & heavy meals, muscle cooling, rest after exercise, thyroxine ingestion
- Duration: hours to days
- Other features: palpitations, sweating, nausea, vomiting, weight loss
- Labs
  - Usually K < 2.5 μmol/L
  - Low TSH
- Treatment
  - Correct thyrotoxicosis
  - Propranolol
  - Potassium
  - NOT Acetazolamide
Non-dystrophic Myotonia (NDM)

- Inherited disorders of skeletal muscle ion channels
  - SCN4A, ClCN1
- Rare disease
Myotonia

- Clinical Myotonia
  - Action myotonia
    - delayed relaxation of muscle after voluntary contraction
  - Paramyotonia
    - worsens with repeated contraction
  - Classic myotonia
    - improves with exercise: “warm-up”
NDM Subtypes

**CLCN1**
- Myotonia Congenita

**SCN4A**
- Paramyotonia congenita
- Sodium channel myotonias
- ACZ-responsive myotonia
  - Myotonia fluctuans
  - Myotonia permanens
- K aggravation
- Cold insensitivity
- No weakness

HyperPP + PMC
<table>
<thead>
<tr>
<th>NDM: sodium channel mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paramyotonia Congenita</strong></td>
</tr>
<tr>
<td>- Paradoxical myotonia</td>
</tr>
<tr>
<td>- Muscular physique</td>
</tr>
<tr>
<td>- Profound cold sensitivity with stiffness &amp; weakness</td>
</tr>
<tr>
<td>- Normal strength</td>
</tr>
<tr>
<td>- Sodium channel mutations (SCNA4)</td>
</tr>
<tr>
<td><strong>Sodium Channel Myotonias (K-aggravated myotonia)</strong></td>
</tr>
<tr>
<td>- Warm-up</td>
</tr>
<tr>
<td>- Sensitive to K⁺</td>
</tr>
<tr>
<td>- NO weakness</td>
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</table>
NDM: chloride channel mutations

- Dominant (Thomsen)
- Recessive (Becker)

Clinical features
- Warm-up phenomenon
- Muscular physique
- 100 CLCN1 mutations
# Myotonia Congenita

<table>
<thead>
<tr>
<th></th>
<th>Thomsen’s MC</th>
<th>Becker’s MC</th>
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<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Infancy</td>
<td>4-12 yrs</td>
</tr>
<tr>
<td><strong>Course</strong></td>
<td>Constant</td>
<td>Progressive</td>
</tr>
<tr>
<td><strong>Weakness</strong></td>
<td>None</td>
<td>Transient weakness</td>
</tr>
<tr>
<td><strong>Muscle hypertrophy</strong></td>
<td>+/-</td>
<td>Present</td>
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<tr>
<td><strong>Myotonia</strong></td>
<td>Generalized</td>
<td>Legs</td>
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Treatment Options in NDM

• No FDA approved Rx

• Off-label use
  • Mexiletine
  • Flecainide
  • Procainamide
  • Phenytoin
  • Quinine
  • Acetazolamide
  • Carbamazepine
Mexiletine for Symptoms and Signs of Myotonia in Nondystrophic Myotonia
A Randomized Controlled Trial

- Type Ib anti-arrhythmic
- Blocks Na channels in cardiac & skeletal muscles
- Mexiletine 200 mg tid
  - Reduced muscle stiffness, weakness, & pain
  - Improved quality of life
  - Reduced myotonia

Statland et al, JAMA. 2012;308(13):1357-1365
### Adverse Events

<table>
<thead>
<tr>
<th>Category</th>
<th>Mexiletine</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Cardiac*</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Constitutional</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Dermatology/Skin</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Gastrointestinal</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lymphatics</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal/Soft Tissue</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Neurologic</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Pain</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>24</strong></td>
<td><strong>11</strong></td>
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Conclusions

- Periodic paralyses & NDM are rare diseases
- Prolonged exercise testing may be normal in PP
- Prolonged exercise test may be abnormal in secondary PP
- Genetic testing may be normal in PP & NDM
- Treatment options are available, but are not a cure
- Dietary & lifestyle changes are critical in PP!