**Neuromuscular disease with abnormal movement**

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**Cramp**

- Episodic and involuntary muscle contraction
- Associated with pain
- Occur in shorten position and contracting muscle
- Motor neuron hyperactivity causing sustained muscle spasm
- Preceded by fasciculations or muscle twitching due to repetitive contractions of motor units
- High frequency discharge (20-150 Hz) on EMG

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**Classification of Cramp**

- **Paraphysiological cramp**
  - Occur in healthy person related to specific physiology circumstances
  - Pregnancy or exercise
  - Hyperexcitability of nerve terminal branches due to continued muscle use

- **Idiopathic**
  - **Sporadic**
    - Cramp-fasciculation syndrome
    - Myokymia-hyperhydrosis syndrome
  - **Inherited**
    - Familial nocturnal cramps

- **Symptomatic cramp**
  - **Hydroelectrolyte disturbances**
    - Hyper- and hyponatremia
    - Dehydration
    - Hypertension, hyperperfusion
    - Hyper- and hypokalemia
    - Hypocalcemia
  - **Endocrine-metabolic condition**
    - Hypothyroidism
    - Hyper- and hypoparathyroidism
    - Uremia and dialysis
    - Cushing's
    - Hyperaldosteronism
Specific muscle diseases associated with myalgia and muscle cramps

- Myotonic dystrophy
- Muscle channelopathies
  - Chloride channel: MC (Becker, Thomsen)
  - Sodium channel: PMC, hyperKPP
  - Calcium channel: hypokPP
- Metabolic myopathies
  - Glycogen metabolism disorder
  - Lipid metabolism disorder

Contracture

- Do not occur at rest
- Develop during exercise
- Related to muscle damage
- Leading to myoglobinuria and acute tubular necrosis
- Electrically silent on EMG

Disorder of glycolytic or glycogenolytic enzyme defect

- McArdle disease
  - Myophosphorylase deficiency
- Tarui disease
  - Phosphofructokinase deficiency
- Exercise intolerance
- Progressive weakness
- Painful contracture

Contracture

- Painful contracture
  - Metabolic myopathy – glucose metabolism
  - Sodium channelopathy – paramyotonia congenita
  - Hypothyroid myopathy
  - Ripping muscle disease
- Painless contracture
  - Spasticity (damage of descending motor pathway) – muscle stiffness, cramps and spasms
  - Prolonged muscle immobilization

McArdle’s disease

- Myalgia and painful muscle cramps
  - Develop within minutes only after forceful exercise
  - Resolve with rest
  - Improve after warm up period of non-exhausting exercise (second wind phenomenon)
- Hand cramp posture (similar to focal dystonia or myotonia)
  - After forearm exercise test for lactate production
  - After performing repetitive gripping movements

Forearm exercise test

- Baseline lactate and ammonia level
  - Isometric handgrip contraction
  - Measure lactate and ammonia level at 1, 2, 4, 6 and 10 minutes
- Normal: 3-5 x elevation of lactate and ammonia within 5 min of exercise and return to baseline level within 30 min
- No elevation of lactate in muscle glycogenosis
Neuromuscular disease with abnormal movement

Hypothyroid myopathy
- Myalgia
- Muscle cramp
- Contractures
- Muscle stiffness and slow movement
- Worsened by cold
- Myoedema

Tetany or capopedal spasm
- Continuous tonic spasm of muscle
- motor unit hyperactivity
- Paraesthesia
- Sensory hyperactivity

Rippling muscle disease
- Painful muscle stiffness, contractures and rippling movement in muscles
- Induced with muscle stretching by either voluntary contraction or percussion
- Myoedema
- Electrically silent on EMG

Caveolinopathy
- Caveolin 3: Component of muscle fibre membrane
  - 4 major phenotypes
    - LGMD 1C
    - Distal Myopathy
    - Raised CK
    - Rippling muscle disease

Myotonia
- Phenomenon of impaired relaxation of the muscle after forceful voluntary contraction
- Repetitive depolarization of muscle membrane
- Warm up phenomenon
- Paramyotonia – worse with cold temperature
- Spontaneous discharges of muscle fibers on EMG
  - waxing and waning of amplitude and frequency with high firing rate between 20-150 Hz

Myotonic disorder
- Acquired myotonia
  - drugs
  - malignancy
- Genetic myotonia
  - Myotonic dystrophy (DM1, 2, 3…)
  - Non-dystrophic myotonia
    - Myotonia congenita (chloride channel)
    - Paramyotonia congenita (sodium channel)
    - Higashi syndrome (sodium channel)
Neuromuscular disease with abnormal movement

Charungthai Dejthevaporn

Myotonia congenita

Clinical features
- Myotonia with warm up phenomenon
- Muscle hypertrophy
- Pain/ stiffness
- Transient weakness
- Dominant Thomson’s • upper > lower limb; early age of onset from 2 years
- Recessive Becker’s • lower limb > upper limb; transient weakness on initiation of movement; muscle hypertrophy; age of onset from 4 years

Myotonia Congenita

<table>
<thead>
<tr>
<th>Features</th>
<th>Thomson’s disease</th>
<th>Becker’s disease</th>
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</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>Dominant</td>
<td>Recessive</td>
</tr>
<tr>
<td>Onset</td>
<td>Infancy or Early childhood</td>
<td>First decade (4-12 years)</td>
</tr>
<tr>
<td>Distribution</td>
<td>Face, arms &gt; legs</td>
<td>Legs &gt; face, arms</td>
</tr>
<tr>
<td>Myotonia</td>
<td>Warm-up phenomenon</td>
<td>Warm-up phenomenon</td>
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<tr>
<td>Precipitants</td>
<td>Rest</td>
<td>Rest</td>
</tr>
<tr>
<td>Additional symptoms</td>
<td>None</td>
<td>Transient, progressive weakness</td>
</tr>
<tr>
<td>Routine EMG</td>
<td>Myotonic discharge</td>
<td>Myotonic discharge</td>
</tr>
<tr>
<td>Cold immersion neuromyology</td>
<td>No CMAP amplitude decrease with cooling</td>
<td>No CMAP amplitude decrease with cooling</td>
</tr>
<tr>
<td>Treatment</td>
<td>Medline, phenytoin</td>
<td>Medline, phenytoin</td>
</tr>
<tr>
<td>Channel affected</td>
<td>CI Channel Ch 7a</td>
<td>CI Channel Ch 7a</td>
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</table>

Paramyotonia Congenita

<table>
<thead>
<tr>
<th>Features</th>
<th>Paramyotonia congenita</th>
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</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>Dominant</td>
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<tr>
<td>Onset</td>
<td>Birth/infancy</td>
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<tr>
<td>Distribution</td>
<td>Face, tongue, arm</td>
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<tr>
<td>Myotonia</td>
<td>Paradoxical worsening</td>
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<td>Precipitants</td>
<td>Cold and exertion</td>
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<tr>
<td>Additional symptoms</td>
<td>Cold induced weakness</td>
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<tr>
<td>Routine EMG</td>
<td>Myotonic discharge</td>
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<tr>
<td>CMAP amplitude</td>
<td>Decrease with cooling</td>
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<tr>
<td>Treatment</td>
<td>Medline, acetazolamide</td>
</tr>
<tr>
<td>Channel affected</td>
<td>No channel</td>
</tr>
</tbody>
</table>

PMC

- associated with episodes of weakness
- as a result of a persistent inward current causing depolarization of the muscle membrane
- overlap with HyperPP
- presence of paradoxical eye closure myotonia - specific

SCM (SCN4A myotonia)

- Painful myotonia is more prevalent and severe
- prominent eyelid/ facial myotonia
- dietary triggers (potassium sensitive myotonia)
- can have neonatal onset
- Neonatal hypotonia
- Neonatal stridor
- Episodic neonatal laryngospasm

Peripheral nerve hyperexcitability syndrome

- Continuous motor unit and muscle fiber activity generated by discharges in motor axon
- Evident at rest and during sleep
- Myokymia
- Clinically visible undulating, wave like or worm-like rippling of muscle
- EMG findings of continuous muscle fiber activity with doublet, triplet, and multiple motor unit discharges
- Fasciculations
- Neuromyotonia
- Repetitive trains of high frequency discharges
- After discharges following voluntary contraction, peripheral nerve stimulation, and gentle percussion of peripheral nerve
- Delayed muscle relaxation
Causes of peripheral nerve hyperexcitability

- Inherited disorders
  - Episodic ataxia type 1 with myokymia (Kv1.1; KCNA1)
  - Benign familial neonatal epilepsy and myokymia
  - KCNQ2
  - Hereditary myokymia without central nervous system features
  - Familial cramp syndrome

- Toxins
  - Acetylcholinesterase inhibitors
  - Gold
  - Toluene
  - Oxaliplatin (Wilson et al., 2002)
  - Timber rattle snake venom
  - Black widow spider venom (α-latrotoxin)
  - Green mamba venom (α-dendrotoxin)

Causes of peripheral nerve hyperexcitability

- Nerve injury
  - Radiation toxicity
  - Inherited neuropathies (CMT II)
  - Inflammatory demyelinating neuropathies
  - Multiple sclerosis (facial myokymia)
  - Conduction block neuropathy
  - Focal compression neuropathy
  - Chronic motor neuron disorders (ALS)
  - Amyloidosis
  - Uremia

Causes of peripheral nerve hyperexcitability

- Autoimmune disorders
  - Acquired neuromyotonia (basal syndrome)
  - Mésan syndrome
  - Charcot-Marie-Tooth syndrome
  - Hereditary myokymia
  - Thymoma (with or without myasthenia gravis)
  - Small cell lung carcinoma

- Associated with other autoimmune conditions
  - Myasthenia gravis
  - Gullain-Barre syndrome or Chronic inflammatory
  - Dehydrating Polyneuropathy (CIDP)
  - Systemic lupus
  - Multiple sclerosis
  - Penicillamine

- Other disorders
  - Benign fasciculation syndrome
  - Benign focal myokymia

Schwartz-Jampel syndrome

- Rare condition presents in childhood with continuous and generalized muscle activity
- Neuromyotonia on EMG
- Skeletal abnormality
- Facial blepharophimosis and dimpling of the chin (caused by continuous contraction of facial muscles)
- Slow movement due to delay muscle relaxation (ongoing muscle activity and after discharges)
- Mutation in the gene encoding the basement membrane protein perlecan that anchors acetylcholinesterase to the synaptic membrane in NMJ
- Persistent cholinergic activation of NMJ
Localised peripheral nerve hyperexcitability
- Focal myokymia and neuromyotonia from radiation
- Hemifacial spasms
- Hemi-masticatory spasms

Hemi-masticatory spasm
- Involuntary painful spasm of jaw closure due to unilateral contraction of temporalis and masseter muscles
- Triggered by chewing or talking
- Trigeminal neuropathy
- Associated with facial hemiatrophy, a localized form of scleroderma (the Parry Romberg syndrome)

Kennedy's disease
- X-linked bulbospinal muscular atrophy
- Age 35-60 years
- Symmetrical proximal muscle weakness
- Perioral fasciculations
- Bulbar dysfunction
- 50% Gynecomastia
- 50% sensory neuropathy
- Postural tremor
- Trinucleotide expansion in the Androgen Receptor (AR) gene
- Polyglutamine expansion in the protein CAG
  - Normal 9-36, mutant 40-62 CAG repeats

Movement disorder syndromes in peripheral neuropathies
- Neuropathic tremor
- Myoclonus
- Dystonia
- Focal dyskinesia
- Painful legs moving toes
- Restless leg syndrome

Stiff person syndrome
- Intermittent muscle stiffness and spasms
  - axial and proximal limb
  - Triggered by external stimuli
- Autoimmune
  - Anti-GAD:
    - Abdomen, neck, and thoracolumbar regions
  - Epileptiform postures
  - Amphiphysin antibodies
  - arm and neck muscle
  - Associated with CA long and breast

Facioscapulohumeral Dystrophy
- Typical clinical characteristic in many patients
- Periscapular weakness
- Beevor's sign (umbilicus move upward when flex trunk due to lower abdominal muscle weakness)
- Variants
  - Very early onset
  - Absence of facial weakness
  - Scapuloperoneal syndrome
  - Presentation with foot drop
  - Asymmetry
  - Unilateral wing scapula (may misdiagnosed as long thoracic neuropathy)
  - Inflammatory biopsy