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 du to repetitive contractions of motor units
- High frequency discharge (20-150 Hz) on EMG

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

Classification of Cramp

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

Classification of Cramp

- **Symptomatic cramp**
  - **CNS :**
    - Multiple sclerosis, Parkinson's disease
  - **PNS :**
    - motor neuron disease, neuropathy, radiculopathy, plexopathy, myopathy
  - **Cardiovascular disease**
    - arterial or venous disease
  - **Toxic/medication**
    - statin, fibrate, diuretic

Classification of Cramp

- **Symptomatic cramp**
  - **Hydroelectrolyte disturbances**
    - hypo-Mg++
    - dehydration
    - Heat cramp, perspiration
    - hyper-hypo Na+, K+, Ca++
  - **Endocrine-metabolic condition**
    - hypo- hyperthyroid
    - hypo-hyperparathyroidism
    - uremia and dialysis
    - cirrhosis
    - hypoadrenalism

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**
  - myophosphorelase deficiency
- **Tarui disease**
  - phosphofructokinase deficiency

- **Exercise intolerance**
- **Progressive weakness**
- **Painful contracture**

Contracture

- **Painful contracture**
  - Metabolic myopathy – glucose metabolism
  - Sodium channelopathy – paramyotonia congenita
  - Hypothyroid myopathy
  - Rippling 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

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)
    - hypoKPP (calcium channel)

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

Features	Thomsen's disease	Becker's disease
Inheritance	Dominant	Recessive
Onset	Infancy or Early childhood	First decade (4-12 years)
Distribution	Face, arms > legs	Legs > face, arms
Myotonia	Warm-up phenomenon	Warm-up phenomenon
Precipitants	Rest	Rest
Additional symptoms	None	Transient; progressive weakness
Routine EMG	Myotonic discharge	Myotonic discharge
Cold immersion neurophysiology	No CMAP amplitude decrement with cooling	No CMAP amplitude decrement with cooling
Treatment	Mexilitine, phenytoin	Mexilitine, phenytoin
Channel affected	Cl^- Channel Ch 7q	Cl^- Channel Ch 7q

Paramyotonia Congenita

Features	Paramyotonia congenita
Inheritance	Dominant
Onset	Birth/infancy
Distribution	Face, tongue, arm
Myotonia	Paradoxical worsening
Precipitants	Cold and exertion
Additional symptoms	Cold induced weakness Some with periodic paralysis
Routine EMG	Myotonic discharge
Cold immersion neurophysiology	CMAP amplitude decrease with cooling
Treatment	Mexilitine, acetazolamide
Channel affected	Na^+ channel

PMC

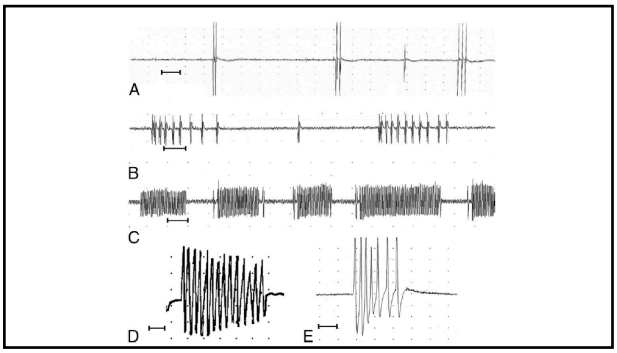
- associated with episodes of weakness
  - as a result of a persistent inward current causing depolarization of the muscle membrane
- overlap with HyperPP
- presence of paradoxical eye closure myotonia - specific

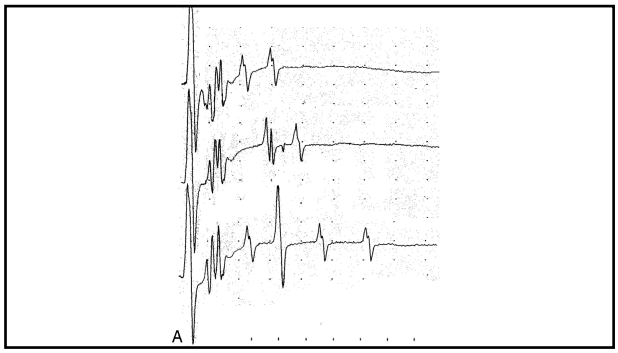
SCM (SCN4A myotonia)

- Painful myotonia is more prevalent and severe
- prominent eyelid/ facial myotonia
- dietary triggers (potassium sensitive myotonias)
- 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 nerve disorders (ALS)
  - Amyloidosis
  - Uremia

Causes of peripheral nerve hyperexcitability

- **Autoimmune disorders**
  - Acquired neuromyotonia (Isaacs syndrome)
  - Morvan syndrome
  - Cramp-fasciculation syndrome
  - Paraneoplastic neuromyotonia
  - Thymoma (with or without myasthenia gravis)
  - Small-cell lung carcinoma
- **Associated with other autoimmune conditions**
  - Myasthenia gravis
  - Guillain–Barre´ syndrome or Chronic Inflammatory
  - Demyelinating 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 memebrane in NMJ
- Persistent cholinergic activation of NMJ

Localized peripheral nerve hyperexcitability

- Focal myokymia and neuromyotonia from radiation
- Hemifacial spasm
- Hemi-masticatory spasm

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 from of scleroderma (the Parry Romberg syndrome)

Kennedy's disease

- X-linked bulbospinal muscular atrophy
- Age 35-60 years
- Symmetrical proximal muscle weakness
- Peri-oral fasciculations
- Bulbar dysfunction
- 50% Gynecomastia
- 50% sensory neuronopathy
- 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
    - Episthotonus posture
  - Amphiphysin antibodies
    - arm and neck muscle
    - Associated with CA lung 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