Myopathies with myotonia or periodic weakness

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Myopathies with myotonia or periodic weakness

Myotonias
Other episodic disorders
Neuromuscular transmission
Myasthenic syndrome
Peripheral nerves
Neuromyotonia
Central nervous system
Epilepsies – idiopathic
Ataxias

Types of ion channels

Structure of voltage gated Na⁺ channels

Function of the Na channel

Function of voltage gated Na⁺ channels

- Generate and propagate action potentials
- Generate current to overcome membrane capacitance
Localization of voltage gated Na+ channels

- In axons nodes of Ranvier
- Initial segments of the axons
- Postsynaptic folds of the neuromuscular junction

Function of voltage gated K+ channels

- Delayed rectifier, repolarization after action potential
- Ca++ sensitive ion channels generate oscillations, afterhyperpolarization
- Regulate resting membrane potential
- Control the shape and frequency of action potentials

Localization of voltage gated K+ channels

- In the axons in the region under the Schwann cell

Structure of voltage gated Ca+ channels

Function of voltage gated Ca+ channels

- L-type: Excitation-contraction coupling in muscle, depolarization,
- N-type: transmitter release
- P-type: transmitter release (MNJ)
- Q-type: transmitter release
- R-type: transmitter release

Function of voltage gated Cl- channels

- Contribute to resting conductance in muscle and nerve cells
**Channel toxins**

- Lidocain
  - Blocks voltage-gated Na⁺ channels
- Conotoxins
  - Bind to Na⁺ and Ca⁺⁺ channels
- Saxitoxin
  - Blocks voltage-gated Na⁺ channels
- Tetrodotoxin
  - Blocks voltage-gated Na⁺ channels

**Channelopathies in neurology**

**Chloride channelopathies in the muscles**

- Myotonia congenita (Thomsen)
- Myotonia congenita (Becker)
- Myotonia levior
- XMEA (X-linked myopathy with excessive autophagy)

**Sodium channelopathies in the muscles**

- Paramyotonia congenita
- Hyperkalemic periodic paralysis
- Myotonia fluctuans
- Myotonia permanens
- Acetazolamide responsive myotonia

**Calcium channelopathies in the muscles**

- Hypokalemic periodic paralysis
- Malignant hypertermia
- Central core disease
- Myasthenic syndrome
- Brody myopathy

**Epilepsies**

- Benign neonatal epilepsy
  - Potassium channel (KCNQ2, KCNQ3)
- Febrile seizures and generalized epilepsy syndrome (GEF+)
  - Sodium channel CN1B on chromosome 19q
- Familial adult myoclonic epilepsy
Ataxias

- Episodic ataxia type 2
  - Ca²⁺ channel
- Episodic ataxia/Myokymia syndrome
  - K⁺ channel
- Progressive ataxia SCA6

Potassium channelopathies in the nerves

- Neuromyotonia

Myotonic disorders

Myotonia - clinical definition

Uncontrolled temporary stiffness of muscle due to transient hyperexcitability of muscle fiber membrane

Myotonia after rest

Myotonia, effect of warm-up
AANEM definition: myotonic discharges

Repetitive discharge at rates of 20 to 80 Hz are of two different types: (1) biphasic (positive negative) spike potentials less than 5 ms in duration resembling fibrillation potentials, (2) positive waves of 5 to 20 ms duration resembling positive sharp waves. Both potential forms are recorded after needle insertion, after voluntary muscle contraction or after muscle percussion, and are due to independent, repetitive discharges of single muscle fibers. The amplitude and frequency of the potentials must both wax and wane to be identified as myotonic discharges. This change produces a characteristic musical sound due to corresponding change in pitch, which has been likened to the sound of a “dive bomber”.

Muscle and Nerve 1987; vol 10

Clinical features of myotonia

- Sustained involuntary muscle contraction following strong muscle contraction
- Effect of exercise
  - Improvement (myotonia congenita, myotonic dystrophy)
  - Aggravation (paramyotonia, myotonia fluctuans)
- Effect of temperature
  - Aggravation by cooling in paramyotonia congenita
- Variation of symptoms over time
  - CI channelopathies usually stable
  - Na channelopathies vary

Clinical classification

- Progressive myopathy and myotonia
  - Myotonic dystrophy type 1 (MD1) and type 2 (MD2)
- Main symptom myotonia
  - Myotonia congenita (Thomsen and Becker)
  - Myotonia fluctuans
- Myotonia and episodic weakness
  - Paramyotonia congenita
- Hyperkalemic periodic paralysis
- Periodic paralysis
  - Hypokalemic periodic paralysis

Myotonic dystrophy type 1 (MD1)

- Genetics
  - Autosomal dominant inheritance
  - Gene location 19q13.2-q13.3
  - Gene product myotolin protein kinase DMPK
  - Expanded CGT trinucleotide repeat in DMPK in normal subjects the length is up to 37 repeats in patients with myotonic dystrophy up to 2000 repeats can be found
  - Severity is related with the number of repeats
  - Reduced amount of DMPK may lead to cell apoptosis

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### MD1 - Clinical features 1
- Most common adult myopathy, prevalence 13/100000
- Male:female = 1:1
- Presentation and onset age variable
- Onset usually in the early teens with distal muscle weakness in arms and legs
- Facial muscles and sternocleidomastoid muscles are also weak, mild ptosis

### MD1 - Pathophysiology
- Reduced DMPK results in Na+ channel abnormalities
- Patients with mainly myotonia tend to have normal resting membrane potential
- Patients with severe dystrophy have reduced resting membrane potential
- Cl- conductance varies from low to low normal
- K+ conductance normal
- Patch clamp studies have shown abnormal inactivation of Na+ channels
- In myotonic muscular dystrophy, abnormal muscle Na+ currents underlie myotonic discharges (Mounsey et al 1995).

### MD1 - Clinical features 2
- Myotonia is usually present and can be demonstrated in the hand muscles
- Patients rarely complain about myotonia (unlike patients with myotonia congenita)
- Myotonia is reduced after exercise "warm-up" effect like myotonia congenita.

### MD1 - Clinical features 3
- Cataracts
- Retinal dysfunction
- CNS, mild mental dysfunction
- Premature balding
- Mild polyneuropathy is sometimes seen
- Endocrine abnormalities
- Smooth muscle dysfunction

### MD1 - EMG findings
- In adults distal muscles usually show myotonic discharges
- Rarely adults with myotonic dystrophy do not have myotonic discharges
- Generally children carrying the genetic defect do not show myotonic discharges
- After the myotonic discharges have disappeared - positive sharp waves and fibrillation potentials
- Short duration, polyphasic MUPs in distal muscles
- Typically dense interference pattern, reduced in advanced stages
MD1 - Neurography
- Nerve conduction studies conduction velocity usually normal
- In 10% mild to moderate reduced motor conduction velocity
- Motor amplitudes low

Congenital MD1
- Sometimes MD1 presents in a congenital form
  - Neonatal respiratory distress
  - Hypotonia
  - Bilateral facial weakness, deformities of the foot
  - Mental retardation, and
- The mother is a carrier of the MD1 mutation
- Children with congenital MD1 do not show myotonic discharges or any significant abnormalities on EMG
- If congenital MD suspected, examine mother

Myotonic dystrophy type 2 (MD2)

MD2 - Genetics
- Autosomal dominant inheritance
- Chromosome 3q21
- ZNF9 gene mutation (sterol regulatory element)
- CCTG repeat sequence, 104-176 base pairs
- RNA has excessive repeats focaly in muscle cell nucleus

MD2 - Clinical features 1
- Onset of symptoms at the age 8 to 60
- Intrafamilial variability large, mild anticipation
- Myotonia varies, clinical myotonia may be absent
- Myotonia worse during pregnancy
- Myotonia has a warm-up effect
- Electrical myotonia decreases with cold and increases after heating
- Mild proximal weakness especially in the legs, develops at the age of 40-50

Proximal myotonic myopathy: a new dominant disorder with myotonia, muscle weakness, and cataracts.
Neurology 1994;44: 1448-1452
### MD2 - Clinical features 2
- Muscle pain is common, often disabling
- Cataracts > 20 years in 100%
- Diabetes in 20%
- Cardiac arrhythmias
- Hearing loss in 20%
- Clinical course is benign
- Mild elevation of CK
- Muscle biopsy shows non-specific myopathic findings

### MD2 - Pathophysiology
- Not clearly understood
- Normal resting membrane potential
- Normal Cl⁻ conductance
- Neurophysiological basis for the myotonia is different from other channelopathies

### MD2 - EMG findings
- Myotonic discharges, especially in distal muscles
- Myotonic discharges may increase if the muscle temperature increases
- MUP analysis normal or mild myopathic abnormalities, especially in proximal muscles

### MD2 - Other findings
- Neurography
  - Sensory neurography normal
  - Motor CV normal, amplitudes low
- Repetitive nerve stimulation
  - Usually no decrement

### Thomsen - Genetics
- Autosomal dominant inheritance
- Mutation of the muscle chloride channel gene CLCN-1 on chromosome 7q35
- Gene product: muscle Cl⁻ channel, ClC-1
- Prevalence 4/100000 (Becker 1957)
- Penetrance 90%
The mutation interferes with Cl\(^-\) ion channel tetramer formation. Cl\(^-\) conductance stabilizes membrane potential, at rest Cl\(^-\) ion movement across the membrane accounts for 70% of the membrane conductance. The chloride conductance in the muscle fiber membrane is reduced resulting in accumulation of K\(^+\) ions in the t-tubules.

Abnormal Na\(^+\) channel reopenings have been demonstrated. The membrane depolarization is prolonged giving rise to spontaneous repeated action potentials. Other factors contribute: Small changes in Na\(^+\) equilibrium may alter myotonia. Na \(^+\) channel modification due to intracellular mechanisms may cause short term alterations.

Onset of symptoms in infancy or early childhood. Persists throughout life. Presentation varies within families. Myotonia is usually mild. "Warm-up". Muscle strength normal, muscles appear hypertrophic. Myotonia may fluctuate over time. Myotonia may be aggravated by \(\beta_2\) agonist drugs (fenoterol) and also \(\beta\) blocking agents. Sometimes diuretic drugs aggravate myotonia. Depolarizing muscle relaxants may cause spasms.

Myotonic discharges, particularly distally. Warming up effect - less myotonia after a period of maximal contraction. Motor unit potential analysis normal.

Decrementing response, especially at high stimulation frequencies (30 Hz) without intratetanic facilitation. Following exercise the amplitude is decreased, reverse to facilitation. Cooling has no effect (in contrast to paramyotonia congenita).
**Myotonia congenita (Becker) - Genetics**
- Autosomal recessive inheritance
- Mutation of the gene CLCN-1 gene on chromosome 7q35
- > 20 point mutations identified
- Most patients are compound heterozygotes
- Gene product: muscle Cl⁻ channel
- Prevalence 2-4/100 000 (Becker 1957)
- Prevalence probably much higher! In Northern Finland 7/100 000. (Baumann et 1998)

**Becker - Pathophysiology**
- Not as clear as for the dominant form
- Inward rectification permits Cl⁻ efflux but no influx
- No physiological mechanism identified for some mutations

**Becker - Clinical features**
- Myotonia manifests at 7-14 years of age
- Persists throughout life
- Myotonia more severe than Thomsen’s
- Normal muscle strength, short period of exercise decreases strength, returns to normal with exercise
- Leg and gluteal muscles are usually hypertrophic
- Weakness is worse in arms, myotonia worse in legs
- Lordosis is common
- Neck, shoulder and arm muscles appear atrophic
- “Warm-up”

**Becker - EMG**
- Myotonic discharges, particularly distally
- MUP analysis may show mild myopathic abnormalities
- Warming up effect - less myotonia after a period of repeated contractions

**Becker - Repetitive nerve stimulation**
- Decrementing response, especially at high stimulation frequencies (30 Hz)
- Following exercise the amplitude is decreased, reverse to facilitation
- Cooling does not affect this in contrast to paramyotonia congenita

**Becker - Carriers**
- Male carriers have myotonic discharges on EMG
- Female carriers do not have myotonic discharges on EMG
Becker - Effect of muscle contraction on force

Paramyotonia congenita

Ricker et al. Transient muscular weakness in severe recessive myotonia. J Neurol 1978;218:253

Paramyotonia congenita - Genetics

- Autosomal dominant inheritance
- Gene SCN4A on chromosome 17q13,1
- Mutation of muscle α-subunit of the sodium channel
- Genetic defect allelic to hyperkalemic periodic paralysis and myotonia fluctuans

Paramyotonia congenita - Pathophysiology

- Disruption of Na+ channel fast inactivation
- Na+ ions continue to leak into cell
- Some mutations disrupt slow Na+ channel inactivation
- Poor inactivation
  - Prolongs action potential
  - Reduces membrane repolarization
    - Mild depolarization (5-20mV) induces myotonia
    - Severe depolarization (>20mV) induces weakness
- Involuntary electrical activity is not the sole reason for paramyotonic stiffness (Ricker et al 1986)

Paramyotonia congenita - Clinical features

- Symptoms present from birth
- Persist throughout life
- Myotonia worsens with exercise
- Cold worsens myotonia
- In warm surroundings usually no action myotonia
- Predilection of face, neck and distal arm muscles
- Weakness after prolonged exercise and cold
- Respiratory muscles not affected
- CK elevated up to 5-10 times normal

Paramyotonia congenita – EMG

- Myotonic discharges in all muscles (much less than other myotonias)
- In warm muscles MUP analysis normal and interference pattern is normal
- Cooling will initially induce repetitive spontaneous motor unit discharges, some authors describe fibrillation like activity in cooled muscles
- With increased cooling myotonia disappears with complete muscle depolarization and paralysis
- With cooling to 20 C the muscle goes into an electrically silent contracture
Paramyotonia congenita – Neurography

- Neurography
  - MCS amplitude is reduced in cooled muscles

Paramyotonia congenita - EMG findings


Neurophysiological tests for the differential diagnosis of myotonia and periodic weakness

- Electromyography Guides Toward Subgroups of Mutations in Muscle Channelopathies

- Protocol for myotonia and episodic weakness

  - Ulnar nerve stimulation at wrist, recording surface electrodes over hypothenar muscles
  - Peroneal nerve stimulation at ankle and recording from the extensor digitorum brevis
  - Skin temperature 32-33 C
  - Start with long exercise test on one side
  - Short exercise test on opposite side followed by old provocation
Short exercise test protocol

- Baseline M wave at rest
- Rep stim 10 stimuli at 3 Hz
- Strong isometric contraction 10-12 sec
- M wave recorded at 10 second intervals for one minute
- 60 second rest
- Repeat three times

Short exercise test

- Control
- Myotonia congenita

Short test in paramyotonia

- Post exercise myotonia (PEM)

Repeated short exercise tests

- Normal subjects
- Hyperkalemic periodic paralysis
- Myotonic congenita
- Paramyotonia congenita

Post exercise myotonia (PEM)

- Paramyotonia congenita 100%
- Myotonia congenita 30%
- Does not disappear during rep stim (unlike in slow channel syndrome and acetylcholine esterase deficiency)
Rep stim in paramyotonia congenita

Long exercise test

Baseline M wave at rest

5 minutes strong isometric contraction every 30 sec 3-4 sec rest

M wave 2 sec after exercise

-1, 2, 3, 4, 5 min

After that every 5 minutes for 45 min

Long exercise test in periodic paralysis

Cold test

Short exercise test at 33 C on the right side

Cooling for 7 minutes with ice packs (12-13 C) on left side

Short exercise test on the left (cold) side
Effect of cold alone

Cold in myotonia congenita

Short repeated exercise test and cold

Effect of cold on sodium channel myotonia

Protocol for evaluation of myotonia
Repetitive nerve stimulation (RNS) in myotonic disorders

Decrement in recessive MC

RNS in myotonias

- Decrement is seen at various stimulation frequencies in recessive myotonia congenita
- Decrement may be seen in dominant myotonia congenita
- In myotonic dystrophy there may be decrement
- Decrement may take some time to develop 20-50 sec of stimulation
- Decrement may be seen at 5-10 Hz stimulation
- Decrement is due to altered muscle fibre excitability

Game over